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(71) Applicant (for all designated States except US): INCYTE GENOMICS, INC. [US/US]; 3160 Porter Drive, Palo Alto, CA 94304 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). TANG, Y., Tom [CN/US]; 4230 Ranwick Court, San Jose, CA 95118 (US). HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive #12, Mountain View, CA 94040 (US). LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA 95054

(US). BANDMAN, Olga [US/US]; 366 Anna Avenue, Mountain View, CA 94043 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US). YANG, Junming [CN/US]; 7125 Bark Lane, San Jose, CA 95129 (US). REDDY, Roopa [IN/US]; 1233 W. McKinley Avenue #3, Sunnyvale, CA 94086 (US). LU, Dyung, Aina, M. [US/US]; 55 Park Belmont Place, San Jose, CA 95136 (US).

(74) Agents: HAMLET-COX, Diana et al.; Incyte Genomics, Inc., 3160 Porter Drive, Palo Alto, CA 94304 (US).

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(54) Title: INTRACELLULAR SIGNALING MOLECULES

(57) Abstract: The invention provides human intracellular signaling molecules (INTRA) and polynucleotides which identify and encode INTRA. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of INTRA.

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INTRACELLULAR SIGNALING MOLECULES

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of intracellular signaling
5 molecules and to the use of these sequences in the diagnosis, treatment, and prevention of cell
proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and
developmental disorders.

BACKGROUND OF THE INVENTION

10 Cell-cell communication is essential for the growth, development, and survival of
multicellular organisms. Cells communicate by sending and receiving molecular signals. An
example of a molecular signal is a growth factor, which binds and activates a specific transmembrane
receptor on the surface of a target cell. The activated receptor transduces the signal intracellularly,
thus initiating a cascade of biochemical reactions that ultimately affect gene transcription and cell
15 cycle progression in the target cell.

Intracellular signaling is the process by which cells respond to extracellular signals
(hormones, neurotransmitters, growth and differentiation factors, etc.) through a cascade of
biochemical reactions that begins with the binding of a signaling molecule to a cell membrane
receptor and ends with the activation of an intracellular target molecule. Intermediate steps in the
20 process involve the activation of various cytoplasmic proteins by phosphorylation via protein kinases,
and their deactivation by protein phosphatases, and the eventual translocation of some of these
activated proteins to the cell nucleus where the transcription of specific genes is triggered. The
intracellular signaling process regulates all types of cell functions including cell proliferation, cell
differentiation, and gene transcription, and involves a diversity of molecules including protein
25 kinases and phosphatases, and second messenger molecules such as cyclic nucleotides, calcium-
calmodulin, inositol, and various mitogens that regulate protein phosphorylation.

Intracellular signaling is carried out by a variety of molecules that promote the transduction
and amplification of the signal. For example, binding of a ligand to a transmembrane receptor
activates membrane-associated intracellular proteins, such as G-proteins. G-proteins mediate both the
30 level of intracellular second messengers, such as cyclic AMP, and the activity of signaling enzymes,
such as phospholipase C. These messengers and enzymes then activate signal transduction pathways,
many of which are mediated by protein kinase cascades. Phosphorylation of proteins in response to
extracellular signals, cell cycle checkpoints, and environmental or nutritional stresses is often
accomplished by transfer of a high energy phosphate from ATP. Second messengers whose effects
35 are mediated by protein kinases include cyclic AMP, cyclic GMP, inositol triphosphate, cyclic ADP

ribose, and calcium/calmodulin. Alternatively, binding of ligand to a transmembrane receptor, such as a receptor tyrosine kinase, triggers the activation of a molecular "switch," such as a monomeric GTPase. In this case, binding of ligand to the receptor activates a catalytic domain in the intracellular portion of the receptor. This activated domain then switches on the activity of monomeric GTPases such as Ras, usually via adaptor proteins.

Cells also respond to changing conditions by switching off signals. Many signal transduction proteins are short-lived and rapidly targeted for degradation by covalent ligation to ubiquitin, a highly conserved small protein. Cells also maintain mechanisms to monitor changes in the concentration of denatured or unfolded proteins in membrane-bound extracytoplasmic compartments, including a transmembrane receptor that monitors the concentration of available chaperone molecules in the endoplasmic reticulum and transmits a signal to the cytosol to activate the transcription of nuclear genes encoding chaperones in the endoplasmic reticulum.

Certain proteins in intracellular signaling pathways serve to link or cluster other proteins involved in the signaling cascade. These proteins are referred to as scaffold, anchoring, or adaptor proteins. (For review, see Pawson, T., and Scott, J.D. (1997) *Science* 278:2075-2080.) As many intracellular signaling proteins such as protein kinases and phosphatases have relatively broad substrate specificities, the adaptors help to organize the component signaling proteins into specific biochemical pathways.

Gangliosides, generally associated with plasma membranes, also participate in signal transduction. Aberrant ganglioside function has been implicated in inflammatory and degenerative diseases within and outside of the nervous system, including Tay-Sachs disease, multiple sclerosis, lupus erythematosus, and insulin-dependent diabetes mellitus (Misasi, R. et al. (1997) *Diabetes Metab. Rev.* 13:163-179).

Many of the above signaling molecules are characterized by the presence of particular domains that promote protein-protein interactions. A sampling of these domains is discussed below, along with other important intracellular messengers.

Intracellular Signaling Second Messenger Molecules

Phospholipid and Inositol-phosphate Signaling

Inositol phospholipids (phosphoinositides) are involved in an intracellular signaling pathway that begins with binding of a signaling molecule to a G-protein linked receptor in the plasma membrane. This leads to the phosphorylation of phosphatidylinositol (PI) residues on the inner side of the plasma membrane to the biphosphate state (PIP₂) by inositol kinases. Simultaneously, the G-protein linked receptor binding stimulates a trimeric G-protein which in turn activates a phosphoinositide-specific phospholipase C- β . Phospholipase C- β then cleaves PIP₂ into two

products, inositol triphosphate (IP_3) and diacylglycerol. These two products act as mediators for separate signaling events. IP_3 diffuses through the plasma membrane to induce calcium release from the endoplasmic reticulum (ER), while diacylglycerol remains in the membrane and helps activate protein kinase C, an STK that phosphorylates selected proteins in the target cell. The calcium response initiated by IP_3 is terminated by the dephosphorylation of IP_3 by specific inositol phosphatases. Cellular responses that are mediated by this pathway are glycogen breakdown in the liver in response to vasopressin, smooth muscle contraction in response to acetylcholine, and thrombin-induced platelet aggregation.

Cyclic Nucleotide Signaling

Cyclic nucleotides (cAMP and cGMP) function as intracellular second messengers to transduce a variety of extracellular signals including hormones, light, and neurotransmitters. In particular, cyclic-AMP dependent protein kinases (PKA) are thought to account for all of the effects of cAMP in most mammalian cells, including various hormone-induced cellular responses. Visual excitation and the phototransmission of light signals in the eye is controlled by cyclic-GMP regulated, Ca^{2+} -specific channels. Because of the importance of cellular levels of cyclic nucleotides in mediating these various responses, regulating the synthesis and breakdown of cyclic nucleotides is an important matter. Thus adenylyl cyclase, which synthesizes cAMP from AMP, is activated to increase cAMP levels in muscle by binding of adrenaline to β -adrenergic receptors, while activation of guanylate cyclase and increased cGMP levels in photoreceptors leads to reopening of the Ca^{2+} -specific channels and recovery of the dark state in the eye. In contrast, hydrolysis of cyclic nucleotides by cAMP and cGMP-specific phosphodiesterases (PDEs) produces the opposite of these and other effects mediated by increased cyclic nucleotide levels. PDEs appear to be particularly important in the regulation of cyclic nucleotides, considering the diversity found in this family of proteins. At least seven families of mammalian PDEs (PDE1-7) have been identified based on substrate specificity and affinity, sensitivity to cofactors, and sensitivity to inhibitory drugs (Beavo, J.A. (1995) *Physiological Reviews* 75:725-48). PDE inhibitors have been found to be particularly useful in treating various clinical disorders. Rolipram, a specific inhibitor of PDE4, has been used in the treatment of depression, and similar inhibitors are undergoing evaluation as anti-inflammatory agents. Theophylline is a nonspecific PDE inhibitor used in the treatment of bronchial asthma and other respiratory diseases (Banner, K.H. and Page, C.P. (1995) *Eur. Respir. J.* 8:996-1000).

Calcium Signaling Molecules

Ca^{+2} is another second messenger molecule that is even more widely used as an intracellular mediator than cAMP. Two pathways exist by which Ca^{+2} can enter the cytosol in response to extracellular signals: One pathway acts primarily in nerve signal transduction where Ca^{+2} enters a nerve terminal through a voltage-gated Ca^{+2} channel. The second is a more ubiquitous pathway in

which Ca^{2+} is released from the ER into the cytosol in response to binding of an extracellular signaling molecule to a receptor. Ca^{2+} directly activates regulatory enzymes, such as protein kinase C, which trigger signal transduction pathways. Ca^{2+} also binds to specific Ca^{2+} -binding proteins (CBPs) such as calmodulin (CaM) which then activate multiple target proteins in the cell including enzymes, membrane transport pumps, and ion channels. CaM interactions are involved in a multitude of cellular processes including, but not limited to, gene regulation, DNA synthesis, cell cycle progression, mitosis, cytokinesis, cytoskeletal organization, muscle contraction, signal transduction, ion homeostasis, exocytosis, and metabolic regulation (Celio, M.R. et al. (1996) Guidebook to Calcium-binding Proteins, Oxford University Press, Oxford, UK, pp. 15-20). Some Ca^{2+} binding proteins are characterized by the presence of one or more EF-hand Ca^{2+} binding motifs, which are comprised of 12 amino acids flanked by α -helices (Celio, supra). The regulation of CBPs has implications for the control of a variety of disorders. Calcineurin, a CaM-regulated protein phosphatase, is a target for inhibition by the immunosuppressive agents cyclosporin and FK506. This indicates the importance of calcineurin and CaM in the immune response and immune disorders (Schwaninger M. et al. (1993) J. Biol Chem. 268:23111-23115). The level of CaM is increased several-fold in tumors and tumor-derived cell lines for various types of cancer (Rasmussen, C.D. and Means, A.R. (1989) Trends in Neuroscience 12:433-438).

The annexins are a family of calcium-binding proteins that associate with the cell membrane (Towle, C.A. and Treadwell, B.V. (1992) J. Biol. Chem. 267:5416-23). Annexins reversibly bind to negatively charged phospholipids (phosphatidylcholine and phosphatidylserine) in a calcium dependent manner. Annexins participate in various processes pertaining to signal transduction at the plasma membrane, including membrane-cytoskeleton interactions, phospholipase inhibition, anticoagulation, and membrane fusion. Annexins contain four to eight repeated segments of about 60 residues. Each repeat folds into five alpha helices wound into a right-handed superhelix.

25 **Signaling Complex Protein Domains**

PDZ domains were named for three proteins in which this domain was initially discovered. These proteins include PSD-95 (postsynaptic density 95), Dlg (Drosophila lethal(1)discs large-1), and ZO-1 (zonula occludens-1). These proteins play important roles in neuronal synaptic transmission, tumor suppression, and cell junction formation, respectively. Since the discovery of these proteins, over sixty additional PDZ-containing proteins have been identified in diverse prokaryotic and eukaryotic organisms. This domain has been implicated in receptor and ion channel clustering and in the targeting of multiprotein signaling complexes to specialized functional regions of the cytosolic face of the plasma membrane. (For review of PDZ domain-containing proteins, see Ponting, C. P. et al. (1997) Bioessays 19:469-479.) A large proportion of PDZ domains are found in the eukaryotic MAGUK (membrane-associated guanylate kinase) protein family, members of which bind to the

intracellular domains of receptors and channels. However, PDZ domains are also found in diverse membrane-localized proteins such as protein tyrosine phosphatases, serine/threonine kinases, G-protein cofactors, and synapse-associated proteins such as syntrophins and neuronal nitric oxide synthase (nNOS). Generally, about one to three PDZ domains are found in a given protein, although
5 up to nine PDZ domains have been identified in a single protein. The glutamate receptor interacting protein (GRIP) contains seven PDZ domains. GRIP is an adaptor that links certain glutamate receptors to other proteins and may be responsible for the clustering of these receptors at excitatory synapses in the brain (Dong, H. et al. (1997) *Nature* 386:279-284).

The SH3 domain is defined by homology to a region of the proto-oncogene c-Src, a
10 cytoplasmic protein tyrosine kinase. SH3 is a small domain of 50 to 60 amino acids that interacts with proline-rich ligands. SH3 domains are found in a variety of eukaryotic proteins involved in signal transduction, cell polarization, and membrane-cytoskeleton interactions. In some cases, SH3 domain-containing proteins interact directly with receptor tyrosine kinases. For example, the SLAP-130 protein is a substrate of the T-cell receptor (TCR) stimulated protein kinase. SLAP-130 interacts
15 via its SH3 domain with the protein SLP-76 to affect the TCR-induced expression of interleukin-2 (Musci, M.A. et al. (1997) *J. Biol. Chem.* 272:11674-11677). Another recently identified SH3 domain protein is macrophage actin-associated tyrosine-phosphorylated protein (MAYP) which is phosphorylated during the response of macrophages to colony stimulating factor-1 (CSF-1) and is likely to play a role in regulating the CSF-1-induced reorganization of the actin cytoskeleton (Yeung,
20 Y.-G. et al. (1998) *J. Biol. Chem.* 273:30638-30642). The structure of SH3 is characterized by two antiparallel beta sheets packed against each other at right angles. This packing forms a hydrophobic pocket lined with residues that are highly conserved between different SH3 domains. This pocket makes critical hydrophobic contacts with proline residues in the ligand (Feng, S. et al. (1994) *Science* 266: 1241-47). Endophilin is an SH3 domain-containing protein implicated in synaptic vesicle
25 endocytosis. (Micheva, K.D. (1997) 272:27239-27245).

A novel domain, called the WW domain, resembles the SH3 domain in its ability to bind proline-rich ligands. This domain was originally discovered in dystrophin, a cytoskeletal protein with direct involvement in Duchenne muscular dystrophy (Bork, P. and Sudol, M. (1994) *Trends Biochem. Sci.* 19:531-533). WW domains have since been discovered in a variety of intracellular signaling
30 molecules involved in development, cell differentiation, and cell proliferation. The structure of the WW domain is composed of beta strands grouped around four conserved aromatic residues, generally tryptophan.

Like SH3, the SH2 domain is defined by homology to a region of c-Src. SH2 domains interact directly with phospho-tyrosine residues, thus providing an immediate mechanism for the
35 regulation and transduction of receptor tyrosine kinase-mediated signaling pathways. For example, as

many as ten distinct SH2 domains are capable of binding to phosphorylated tyrosine residues in the activated PDGF receptor, thereby providing a highly coordinated and finely tuned response to ligand-mediated receptor activation. (Reviewed in Schaffhausen, B. (1995) *Biochem. Biophys. Acta.* 1242:61-75.)

5 Homer is a neuronal immediate early gene that is enriched at excitatory synapses (Xiao, B. et al. (1998) *Neuron* 21:707-716). Homer proteins form multivalent complexes that bind proline-rich motifs in group I metabotropic glutamate receptors and inositol triphosphate receptors, thereby coupling these receptors in a signaling complex (Tu, J.C. (1999) *Neuron* 23:583-592).

 The pleckstrin homology (PH) domain was originally identified in pleckstrin, the
10 predominant substrate for protein kinase C in platelets. Since its discovery, this domain has been identified in over 90 proteins involved in intracellular signaling or cytoskeletal organization. Proteins containing the pleckstrin homology domain include a variety of kinases, phospholipase-C isoforms, guanine nucleotide release factors, and GTPase activating proteins. For example, members of the FGD1 family contain both Rho-guanine nucleotide exchange factor (GEF) and PH domains, as well
15 as a FYVE zinc finger domain. FGD1 is the gene responsible for faciogenital dysplasia, an inherited skeletal dysplasia (Pasteris, N.G. and Gorski, J.L. (1999) *Genomics* 60:57-66). Many PH domain proteins function in association with the plasma membrane, and this association appears to be mediated by the PH domain itself. PH domains share a common structure composed of two antiparallel beta sheets flanked by an amphipathic alpha helix. Variable loops connecting the
20 component beta strands generally occur within a positively charged environment and may function as ligand binding sites (Lemmon, M. A. et al. (1996) *Cell* 85:621-624.). n-Chimaerin is a GAP involved in the formation of lamellipodia and filopodia in neuroblastoma cells. (Kozma, R. et al. (1996) *Mol. Cell Biol.* 16:5069-5080.)

 Ankyrin (ANK) repeats mediate protein-protein interactions associated with diverse
25 intracellular signaling functions. For example, ANK repeats are found in proteins involved in cell proliferation such as kinases, kinase inhibitors, tumor suppressors, and cell cycle control proteins. (See, for example, Kalus, W. et al. (1997) *FEBS Lett.* 401:127-132; Ferrante, A. W. et al. (1995) *Proc. Natl. Acad. Sci. USA* 92:1911-1915.) These proteins generally contain multiple ANK repeats, each composed of about 33 amino acids. Myotrophin is an ANK repeat protein that plays a key role
30 in the development of cardiac hypertrophy, a contributing factor to many heart diseases. Structural studies show that the myotrophin ANK repeats, like other ANK repeats, each form a helix-turn-helix core preceded by a protruding "tip." These tips are of variable sequence and may play a role in protein-protein interactions. The helix-turn-helix region of the ANK repeats stack on top of one another and are stabilized by hydrophobic interactions (Yang, Y. et al. (1998) *Structure* 6:619-626).

35 The tetratricopeptide repeat (TPR) is a 34 amino acid repeated motif found in organisms

from bacteria to humans. TPRs are predicted to form amphipathic helices, and appear to mediate protein-protein interactions. TPR domains are found in CDC16, CDC23, and CDC27, members the anaphase promoting complex which targets proteins for degradation at the onset of anaphase. Other processes involving TPR proteins include cell cycle control, transcription repression, stress
 5 response, and protein kinase inhibition. (Lamb, J.R. et al. (1995) Trends Biochem. Sci. 20:257-259.)

The armadillo/beta-catenin repeat is a 42 amino acid motif which forms a superhelix of alpha helices when tandemly repeated. The structure of the armadillo repeat region from beta-catenin revealed a shallow groove of positive charge on one face of the superhelix, which is a potential binding surface. The armadillo repeats of beta-catenin, plakoglobin, and p120^{cas} bind the cytoplasmic
 10 domains of cadherins. Beta-catenin/cadherin complexes are targets of regulatory signals that govern cell adhesion and mobility. (Huber, A.H. et al. (1997) Cell 90:871-882.)

The discovery of new intracellular signaling proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, autoimmune/inflammatory, reproductive, and
 15 developmental disorders.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, intracellular signaling molecules, referred to collectively as "INTRA" and individually as "INTRA-1," "INTRA-2," "INTRA-3," "INTRA-4,"
 20 "INTRA-5," "INTRA-6," "INTRA-7," "INTRA-8," "INTRA-9," "INTRA-10," "INTRA-11," "INTRA-12," "INTRA-13," "INTRA-14," "INTRA-15," "INTRA-16," "INTRA-17," "INTRA-18," "INTRA-19," "INTRA-20," "INTRA-21," "INTRA-22," "INTRA-23," "INTRA-24," "INTRA-25," "INTRA-26," "INTRA-27," "INTRA-28," "INTRA-29," "INTRA-30," "INTRA-31," "INTRA-32," "INTRA-33," "INTRA-34," "INTRA-35," "INTRA-36," "INTRA-37," "INTRA-38," "INTRA-39,"
 25 "INTRA-40," "INTRA-41," "INTRA-42," "INTRA-43," "INTRA-44," "INTRA-45," "INTRA-46," "INTRA-47," "INTRA-48," "INTRA-49," "INTRA-50," "INTRA-51," and "INTRA-52." In one aspect, the invention provides an isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an
 30 amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-52.

35 The invention further provides an isolated polynucleotide encoding a polypeptide comprising

an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-52. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:53-104.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a pharmaceutical composition comprising an effective amount of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence

selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and a pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The invention additionally

5 provides a method of treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a)

10 an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The

15 method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a

20 patient in need of such treatment the pharmaceutical composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence

25 selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical

30 composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention further provides a method of screening for a compound that specifically binds

35 to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an

amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:53-104, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding INTRA.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of INTRA.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases,

disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding INTRA were isolated.

5 Table 5 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

10 Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

15 It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

20 Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing
25 the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"INTRA" refers to the amino acid sequences of substantially purified INTRA obtained from
30 any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of INTRA. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of INTRA either by directly interacting with
35 INTRA or by acting on components of the biological pathway in which INTRA participates.

An "allelic variant" is an alternative form of the gene encoding INTRA. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding INTRA include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as INTRA or a polypeptide with at least one functional characteristic of INTRA. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding INTRA, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding INTRA. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent INTRA. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of INTRA is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of INTRA. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of INTRA either by directly interacting with INTRA or by acting on components of the biological pathway in which

INTRA participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind INTRA polypeptides can be prepared using intact polypeptides or using
5 fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize
10 the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures
15 on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as
20 phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring
25 nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic"
30 refers to the capability of the natural, recombinant, or synthetic INTRA, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement,
35 3'-TCA-5'.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution.

Compositions comprising polynucleotide sequences encoding INTRA or fragments of INTRA may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (PE Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
25	Asp	Asn, Glu
	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
30	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
35	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
	Thr	Ser, Val
	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
40	Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide

backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the
5 absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule.
10 A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

15 A "fragment" is a unique portion of INTRA or the polynucleotide encoding INTRA which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10,
20 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the
25 specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:53-104 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:53-104, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:53-104 is useful, for
30 example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:53-104 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:53-104 and the region of SEQ ID NO:53-104 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-52 is encoded by a fragment of SEQ ID NO:53-104. A
35 fragment of SEQ ID NO:1-52 comprises a region of unique amino acid sequence that specifically

identifies SEQ ID NO:1-52. For example, a fragment of SEQ ID NO:1-52 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-52. The precise length of a fragment of SEQ ID NO:1-52 and the region of SEQ ID NO:1-52 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A "full-length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full-length" polynucleotide sequence encodes a "full-length" polypeptide sequence.

"Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn." that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to

compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

5 *Penalty for mismatch: -2*

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 11

10 *Filter: on*

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous
15 nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes
20 in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some
25 alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e
30 sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

35 Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise

comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (Apr-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

5 *Open Gap: 11 and Extension Gap: 1 penalties*

Gap x drop-off: 50

Expect: 10

Word Size: 3

Filter: on

10 Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment
15 length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for chromosome replication, segregation and maintenance.

20 The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific
25 hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive
30 conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

35 Generally, stringency of hybridization is expressed, in part, with reference to the temperature

under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and
5 conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS,
10 for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular
15 circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid
20 sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

25 The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect
30 cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of INTRA which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of INTRA which is useful in any of the antibody production methods disclosed herein or known in
35 the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

5 The term "modulate" refers to a change in the activity of INTRA. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of INTRA.

10 The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

15 "Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

20 "Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

25 "Post-translational modification" of an INTRA may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of INTRA.

30 "Probe" refers to nucleic acid sequences encoding INTRA, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

35 Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also

be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

5 Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al., 1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs
10 can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

 Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to
15 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from
20 megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection
25 programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both
30 unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

35 A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence

that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have
5 been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a
10 vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription,
15 translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

20 An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic
25 acids encoding INTRA, or fragments thereof, or INTRA itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or
30 synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

35 The term "substantially purified" refers to nucleic acid or amino acid sequences that are

removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides
5 by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

10 A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

"Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid
15 sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well
20 as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor
25 of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants, and animals. The isolated DNA of the present invention can be
30 introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having
35 at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of

the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human intracellular signaling molecules (INTRA), the polynucleotides encoding INTRA, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding INTRA. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each INTRA were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. In some cases, GenBank sequence identifiers are also shown in column 5. The Incyte clones and GenBank cDNA sequences, where indicated, in column 5 were used to assemble the consensus nucleotide sequence of each INTRA and are useful as fragments in

hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis along with relevant citations, all of which are expressly incorporated by reference herein in their entirety; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding INTRA. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:53-104 and to distinguish between SEQ ID NO:53-104 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express INTRA as a fraction of total tissues expressing INTRA. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing INTRA as a fraction of total tissues expressing INTRA. Column 5 lists the vectors used to subclone each cDNA library. Of particular interest is the expression of SEQ ID NO:88 and SEQ ID NO:94 in reproductive tissues, of SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:103 in hematopoietic/immune tissues, and of SEQ ID NO:96 in cardiovascular tissues.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding INTRA were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

SEQ ID NO:58 maps to chromosome 7 within the interval from 84.40 to 90.30 centiMorgans. This interval also contains an EST with high similarity to thyroid disease hypothetical autoantigen. SEQ ID NO:67 maps to chromosome 16 within the interval from 119.20 centiMorgans to q-terminus. This interval also contains the paraplegin gene, mutations in which cause spastic paraplegia and OXPHOS impairment. SEQ ID NO:70 maps to chromosome 11 within the interval from 59.50 to 62.50 centiMorgans. SEQ ID NO:71 maps to chromosome 7 within the interval from 138.0 to 145.8 centiMorgans. SEQ ID NO:73 maps to chromosome 12 within the interval from 76.5 to 84.2 centiMorgans. SEQ ID NO:77 maps to chromosome 7 within the interval from 4.8 to 10.6 centiMorgans and to chromosome 4 within the interval from 56.7 to 60.5 centiMorgans. The interval

on chromosome 7 from 4.8 to 10.6 centiMorgans also contains a gene associated with cell proliferation. The interval on chromosome 4 from 56.7 to 60.5 centiMorgans also contains a gene associated with cell proliferation. SEQ ID NO:79 maps to chromosome 15 within the interval from 32.2 to 47.1 centiMorgans. This interval also contains a gene associated with cell proliferation. SEQ ID NO:80 maps to chromosome 20 within the interval from 50.2 to 53.6 centiMorgans. This interval also contains a gene associated with cell differentiation. SEQ ID NO:84 maps to chromosome 3 within the interval from 142.2 to 148.7 centiMorgans. SEQ ID NO:87 maps to chromosome 5 within the interval from 141.4 to 147.1 centiMorgans. SEQ ID NO:91 maps to chromosome 12 within the interval from 62.7 to 67.3 centiMorgans. SEQ ID NO:95 maps to chromosome 15 within the interval from 45.5 to 58.8 centiMorgans. SEQ ID NO:97 maps to the X chromosome within the interval from 112.8 to 139.4 centiMorgans.

The invention also encompasses INTRA variants. A preferred INTRA variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the INTRA amino acid sequence, and which contains at least one functional or structural characteristic of INTRA.

The invention also encompasses polynucleotides which encode INTRA. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:53-104, which encodes INTRA. The polynucleotide sequences of SEQ ID NO:53-104, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding INTRA. In particular, such a variant polynucleotide sequence will have at least about 80%, or alternatively at least about 90%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding INTRA. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:53-104 which has at least about 80%, or alternatively at least about 90%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:53-104. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of INTRA.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding INTRA, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These

combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring INTRA, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode INTRA and its variants are generally capable
5 of hybridizing to the nucleotide sequence of the naturally occurring INTRA under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding INTRA or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with
10 which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding INTRA and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode INTRA and
15 INTRA derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding INTRA or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of
20 hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:53-104 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

25 Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (PE Biosystems, Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found
30 in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (PE Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (PE Biosystems), the MEGABACE 1000 DNA sequencing
35 system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting

sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

- 5 The nucleic acid sequences encoding INTRA may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) *PCR Methods Applic.* 2:318-322.)
- 10 Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) *Nucleic Acids Res.* 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom,
- 15 M. et al. (1991) *PCR Methods Applic.* 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries
- 20 (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of
- 25 about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence

30 into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the

35 emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate

software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, PE Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

5 In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode INTRA may be cloned in recombinant DNA molecules that direct expression of INTRA, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express INTRA.

10 The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter INTRA-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction
15 sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat.
20 Biotechnol. 17:259-264; and Crameri, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of INTRA, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired
25 properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of
30 homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding INTRA may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids
35 Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.)

Alternatively, INTRA itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins. Structures and Molecular Properties, WH Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) *Science* 269:202-204.) Automated synthesis
5 may be achieved using the ABI 431A peptide synthesizer (PE Biosystems). Additionally, the amino acid sequence of INTRA, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid
10 chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) *Methods Enzymol.* 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, supra, pp. 28-53.)

In order to express a biologically active INTRA, the nucleotide sequences encoding INTRA or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which
15 contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding INTRA. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences
20 encoding INTRA. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding INTRA and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG
25 initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression
30 vectors containing sequences encoding INTRA and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and
35 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding INTRA. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus);

5 plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; Scorer, C.A. et al. (1994) Bio/Technology 12:181-184; Engelhard, E.K. et al. (1994) Proc. Natl.

10 Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO J. 6:307-311; Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington,

15 J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al., (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al.

20 (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding INTRA. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding INTRA can be achieved using a

25 multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPO1 plasmid (Life Technologies). Ligation of sequences encoding INTRA into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of

30 nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of INTRA are needed, e.g. for the production of antibodies, vectors which direct high level expression of INTRA may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of INTRA. A number of vectors

35 containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH

promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Bitter, supra; and Scorer, supra.)

5 Plant systems may also be used for expression of INTRA. Transcription of sequences encoding INTRA may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, supra; Broglie, supra; and Winter, supra.) These
10 constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding INTRA may be ligated into
15 an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses INTRA in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-
20 based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet.
25 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of INTRA in cell lines is preferred. For example, sequences encoding INTRA can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector.
30 Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk⁻* and *ap^r* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding INTRA is inserted within a marker gene sequence, transformed cells containing sequences encoding INTRA can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding INTRA under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding INTRA and that express INTRA may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of INTRA using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on INTRA is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and

Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled
5 hybridization or PCR probes for detecting sequences related to polynucleotides encoding INTRA include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding INTRA, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase
10 such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

15 Host cells transformed with nucleotide sequences encoding INTRA may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode INTRA may be designed to contain signal sequences which
20 direct secretion of INTRA through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a “prepro” or
25 “pro” form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

30 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding INTRA may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric INTRA protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of INTRA activity. Heterologous protein
35 and peptide moieties may also facilitate purification of fusion proteins using commercially available

affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the INTRA encoding sequence and the heterologous protein sequence, so that INTRA may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled INTRA may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ³⁵S-methionine.

INTRA of the present invention or fragments thereof may be used to screen for compounds that specifically bind to INTRA. At least one and up to a plurality of test compounds may be screened for specific binding to INTRA. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of INTRA, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which INTRA binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express INTRA, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing INTRA or cell membrane fractions which contain INTRA are then contacted with a test compound and binding, stimulation, or inhibition of activity of either INTRA or the compound is analyzed.

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with INTRA, either in

solution or affixed to a solid support, and detecting the binding of INTRA to the compound. Alternatively, the assay may detect or measure binding of a test compound in the presence of a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

INTRA of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of INTRA. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for INTRA activity, wherein INTRA is combined with at least one test compound, and the activity of INTRA in the presence of a test compound is compared with the activity of INTRA in the absence of the test compound. A change in the activity of INTRA in the presence of the test compound is indicative of a compound that modulates the activity of INTRA. Alternatively, a test compound is combined with an in vitro or cell-free system comprising INTRA under conditions suitable for INTRA activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of INTRA may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding INTRA or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding INTRA may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate

into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

Polynucleotides encoding INTRA can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding INTRA is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress INTRA, e.g., by secreting INTRA in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of INTRA and intracellular signaling molecules. In addition, the expression of INTRA is closely associated with cancers of the hematopoietic/immune, nervous, gastrointestinal, and reproductive, systems therefore, INTRA appears to play a role in cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders. In the treatment of disorders associated with increased INTRA expression or activity, it is desirable to decrease the expression or activity of INTRA. In the treatment of disorders associated with decreased INTRA expression or activity, it is desirable to increase the expression or activity of INTRA.

Therefore, in one embodiment, INTRA or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, hematopoietic cancer including lymphoma, leukemia, and myeloma; and other cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, adenoma, carcinoma and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's

disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or

5 pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a gastrointestinal

10 disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis,

15 passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha,-

20 antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and a hepatic tumor including a nodular hyperplasia, a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's

25 disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases

30 including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord

35 diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system

disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a gastrointestinal disorder such as

5 esophagitis, esophageal carcinoma, gastritis, gastric carcinoma, inflammatory bowel disease, cholecystitis, infections of the intestinal tract, pancreatitis, pancreatic carcinoma, cirrhosis, hepatitis, hepatoma, colitis, colonic carcinoma, and Crohn's disease.

In another embodiment, a vector capable of expressing INTRA or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased

10 expression or activity of INTRA including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified INTRA in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA including, but not limited to, those provided above.

15 In still another embodiment, an agonist which modulates the activity of INTRA may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA including, but not limited to, those listed above.

In a further embodiment, an antagonist of INTRA may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of INTRA. Examples of such

20 disorders include, but are not limited to, those cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders described above. In one aspect, an antibody which specifically binds INTRA may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express INTRA.

25 In an additional embodiment, a vector expressing the complement of the polynucleotide encoding INTRA may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of INTRA including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate

30 therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of INTRA may be produced using methods which are generally known in the art. In particular, purified INTRA may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind INTRA. Antibodies to INTRA may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with INTRA or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to INTRA have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of INTRA amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to INTRA may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce INTRA-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

5 Antibody fragments which contain specific binding sites for INTRA may also be generated. For example, such fragments include, but are not limited to, F(ab')₂ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. 10 et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between INTRA and its 15 specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering INTRA epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for INTRA. Affinity is expressed as an 20 association constant, K_a , which is defined as the molar concentration of INTRA-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple INTRA epitopes, represents the average affinity, or avidity, of the antibodies for INTRA. The K_a determined for a preparation of monoclonal antibodies, which are monospecific 25 for a particular INTRA epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the INTRA-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of INTRA, 30 preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For 35 example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml,

preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of INTRA-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al., supra.)

5 In another embodiment of the invention, the polynucleotides encoding INTRA, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding INTRA. Such technology is well known in the art, and antisense oligonucleotides or larger
10 fragments can be designed from various locations along the coding or control regions of sequences encoding INTRA. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

 In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered
15 intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) J. Allergy Clin. Immunol. 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) Blood
20 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) Pharmacol. Ther. 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) Br. Med. Bull. 51(1):217-225; Boado, R.J. et al. (1998) J. Pharm. Sci. 87(11):1308-1315; and Morris, M.C. et al. (1997) Nucleic Acids Res. 25(14):2730-2736.)

25 In another embodiment of the invention, polynucleotides encoding INTRA may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency
30 (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassamias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and Somia, N. (1997) Nature 389:239-242)), (ii)
35 express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated

cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides
 5 brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in INTRA expression or regulation causes disease, the expression of INTRA from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in
 10 INTRA are treated by constructing mammalian expression vectors encoding INTRA and introducing these vectors by mechanical means into INTRA-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev.
 15 Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 9:445-450).

Expression vectors that may be effective for the expression of INTRA include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF,
 20 PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). INTRA may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β -actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. U.S.A. 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998)
 25 Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and H.M. Blau, supra), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding INTRA from a normal individual.

30 Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al.

(1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to INTRA expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding INTRA under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. U.S.A. 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4⁺ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. U.S.A. 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding INTRA to cells which have one or more genetic abnormalities with respect to the expression of INTRA. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu. Rev. Nutr. 19:511-544; and Verma, I.M. and N. Somia (1997) Nature 18:389:239-242, both incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding INTRA to target cells which have one or more genetic abnormalities with

respect to the expression of INTRA. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing INTRA to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has
5 been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye Res. 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a
10 cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) J. Virol. 73:519-532 and Xu, H. et al. (1994) Dev. Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple
15 plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding INTRA to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based
20 on the SFV genome (Garoff, H. and K.-J. Li (1998) Curr. Opin. Biotech. 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full-length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity
25 (e.g., protease and polymerase). Similarly, inserting the coding sequence for INTRA into the alphavirus genome in place of the capsid-coding region results in the production of a large number of INTRA-coding RNAs and the synthesis of high levels of INTRA in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN)
30 indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of INTRA into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA

transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding INTRA.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding INTRA. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs

and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

5 An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding INTRA. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-
10 macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased INTRA expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding INTRA may be therapeutically useful, and in the treatment of disorders
15 associated with decreased INTRA expression or activity, a compound which specifically promotes expression of the polynucleotide encoding INTRA may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in
20 altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding INTRA is exposed to at least one test compound thus obtained. The sample
25 may comprise, for example, an intact or permeabilized cell, or an in vitro cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding INTRA are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding INTRA. The amount of hybridization may be quantified, thus
30 forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a Schizosaccharomyces pombe gene expression
35 system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids

Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruce, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruce, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such pharmaceutical compositions may consist of INTRA, antibodies to INTRA, and mimetics, agonists, antagonists, or inhibitors of INTRA.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Pharmaceutical compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton, J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of pharmaceutical compositions may be prepared for direct intracellular
5 delivery of macromolecules comprising INTRA or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, INTRA or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system
10 (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and
15 routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example INTRA or fragments thereof, antibodies of INTRA, and agonists, antagonists or inhibitors of INTRA, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by
20 calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such
25 compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the
30 active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular
35 formulation.

Normal dosage amounts may vary from about 0.1 μ g to 100,000 μ g, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their
5 inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind INTRA may be used for the diagnosis of disorders characterized by expression of INTRA, or in assays to monitor patients being
10 treated with INTRA or agonists, antagonists, or inhibitors of INTRA. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for INTRA include methods which utilize the antibody and a label to detect INTRA in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A
15 wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring INTRA, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INTRA expression. Normal or standard values for INTRA expression are established by combining body fluids or cell extracts
20 taken from normal mammalian subjects, for example, human subjects, with antibody to INTRA under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of INTRA expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding INTRA may be used
25 for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of INTRA may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess
30 expression of INTRA, and to monitor regulation of INTRA levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding INTRA or closely related molecules may be used to identify nucleic acid sequences which encode INTRA. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a
35 conserved motif, and the stringency of the hybridization or amplification will determine whether the

probe identifies only naturally occurring sequences encoding INTRA, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the INTRA encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:53-104 or from genomic sequences including promoters, enhancers, and introns of the INTRA gene.

Means for producing specific hybridization probes for DNAs encoding INTRA include the cloning of polynucleotide sequences encoding INTRA or INTRA derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding INTRA may be used for the diagnosis of disorders associated with expression of INTRA. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, hematopoietic cancer including lymphoma, leukemia, and myeloma; and other cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, adenoma, carcinoma and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal

circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma ; and a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal

5 obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic

10 obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, α_1 -antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of

15 pregnancy, and a hepatic tumor including a nodular hyperplasia, a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial

20 and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental

25 retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic

30 disorders, akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a gastrointestinal disorder such as esophagitis, esophageal carcinoma, gastritis, gastric carcinoma, inflammatory bowel disease, cholecystitis, infections of the intestinal tract, pancreatitis, pancreatic carcinoma, cirrhosis, hepatitis, hepatoma, colitis, colonic carcinoma, and Crohn's disease. The polynucleotide sequences encoding

35 INTRA may be used in Southern or northern analysis, dot blot, or other membrane-based

technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered INTRA expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding INTRA may be useful in assays that
5 detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding INTRA may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to
10 a control sample then the presence of altered levels of nucleotide sequences encoding INTRA in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of
15 INTRA, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding INTRA, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified
20 polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the
25 patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the
30 development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding
35 INTRA may involve the use of PCR. These oligomers may be chemically synthesized, generated

enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding INTRA, or a fragment of a polynucleotide complementary to the polynucleotide encoding INTRA, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or

5 quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding INTRA may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded

10 conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding INTRA are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and

15 these differences are detectable using gel electrophoresis in non-denaturing gels. In fSSCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed *in silico* SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual overlapping DNA fragments which assemble into a common consensus

20 sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of INTRA include radiolabeling

25 or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) *J. Immunol. Methods* 159:235-244; Duplaa, C. et al. (1993) *Anal. Biochem.* 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives

30 rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript

35 Analysis," U.S. Patent No. 5,840,484, incorporated herein by reference. The microarray may also be

used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information
5 may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, antibodies specific for INTRA, or INTRA or fragments thereof may
10 be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al.
15 (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding INTRA may be
20 used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific
25 region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be
30 used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, e.g., Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic
35 map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man

(OMIM) World Wide Web site. Correlation between the location of the gene encoding INTRA on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as
5 linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely
10 localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

15 In another embodiment of the invention, INTRA, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between INTRA and the agent being tested may be measured.

20 Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with INTRA, or fragments thereof, and washed. Bound INTRA is then detected by methods well known in the art. Purified INTRA can
25 also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding INTRA specifically compete with a test compound for binding INTRA.
30 In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with INTRA.

In additional embodiments, the nucleotide sequences which encode INTRA may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such
35 properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

5 The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/139,566 (filing date 16 June 1999), U.S. Ser. No. 60/149,640 (filing date 17 August 1999), and U.S. Ser. No. 60/164,417 (filing date 9 November 1999), are hereby expressly incorporated by reference.

10 **EXAMPLES**

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a
15 monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A⁺) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUEScript plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), pcDNA2.1 plasmid (Invitrogen, Carlsbad CA), or pINCy plasmid (Incyte Genomics, Palo Alto CA). Recombinant

plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo
5 excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1
10 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically
15 using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation
20 such as the ABI CATALYST 800 (PE Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems). Electrophoretic
25 separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (PE Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit
30 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VI.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable
35 descriptions, references, and threshold parameters. The first column of Table 5 shows the tools,

programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:53-104. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is

much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum \{length(Seq. 1), length(Seq. 2)\}}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding INTRA occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Chromosomal Mapping of ABBR Encoding Polynucleotides

The cDNA sequences which were used to assemble SEQ ID NO:8-14 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:8-14 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for

Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO., to that map location.

The genetic map locations of SEQ ID NO:8-14 [fill in the specific SEQ ID NOs if not all of the sequences have been mapped] are described in The Invention as ranges, or intervals, of human chromosomes. [Include the following sentence if any of your sequences have more than one map location.] More than one map location is reported for SEQ ID NO:8-14 [fill in specific SEQ ID NO:s], indicating that previously mapped sequences having similarity, but not complete identity, to SEQ ID NO:8-14 [fill in specific SEQ ID NO:s] were assembled into their respective clusters. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (<http://www.ncbi.nlm.nih.gov/genemap/>), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

VI. Extension of INTRA Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:53-104 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$, and β -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C,

2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

5 The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the
10 concentration of DNA. A 5 µl to 10 µl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

 The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and
15 sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site
20 overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

 The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following
25 parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing
30 primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems).

 In like manner, the polynucleotide sequences of SEQ ID NO:53-104 are used to obtain 5' regulatory sequences using the procedure above, along with oligonucleotides designed for such extension, and an appropriate genomic library.

35 **VII. Labeling and Use of Individual Hybridization Probes**

Hybridization probes derived from SEQ ID NO:53-104 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μ Ci of [γ - 32 P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

VIII. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Skena (1999), supra). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Skena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645; Marshall, A. and J. Hodgson (1998) Nat. Biotechnol. 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a

fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorption and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is

5 described in detail below.

Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)⁺ RNA is purified using the oligo-(dT) cellulose method. Each poly(A)⁺ RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/ μ l oligo-(dT) primer (21mer), 1X
10 first strand buffer, 0.03 units/ μ l RNase inhibitor, 500 μ M dATP, 500 μ M dGTP, 500 μ M dTTP, 40 μ M dCTP, 40 μ M dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)⁺ RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)⁺ RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37 °C for 2 hr, each reaction sample (one
15 with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85 °C to stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is
20 then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 μ l 5X SSC/0.2% SDS.

Microarray Preparation

Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification
25 uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 μ g. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope
30 slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. 1 μ l of the array element DNA, at an average concentration of 100 ng/ μ l, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

- 5 Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60 °C followed by washes in 0.2% SDS and distilled water as before.

10 Hybridization

- Hybridization reactions contain 9 μ l of sample mixture consisting of 0.2 μ g each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65 °C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm² coverslip. The arrays are transferred to a waterproof chamber having a cavity just
- 15 slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 μ l of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60 °C. The arrays are washed for 10 min at 45 °C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45 °C in a second wash buffer (0.1X SSC), and dried.

20 Detection

- Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide
- 25 containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

- In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477,
- 30 Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples
5 from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital
10 (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping
15 emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

20 IX. Complementary Polynucleotides

Sequences complementary to the INTRA-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring INTRA. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are
25 designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of INTRA. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the INTRA-encoding transcript.

30 X. Expression of INTRA

Expression and purification of INTRA is achieved using bacterial or virus-based expression systems. For expression of INTRA in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid
35 promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory

element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express INTRA upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of INTRA in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding INTRA by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, INTRA is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from INTRA at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified INTRA obtained by these methods can be used directly in the assays shown in Examples XI, XII, and XV.

XI. Demonstration of INTRA Activity

INTRA activity is associated with its ability to form protein-protein complexes and is measured by its ability to regulate growth characteristics of NIH3T3 mouse fibroblast cells. A cDNA encoding INTRA is subcloned into an appropriate eukaryotic expression vector. This vector is transfected into NIH3T3 cells using methods known in the art. Transfected cells are compared with non-transfected cells for the following quantifiable properties: growth in culture to high density, reduced attachment of cells to the substrate, altered cell morphology, and ability to induce tumors when injected into immunodeficient mice. The activity of INTRA is proportional to the extent of increased growth or frequency of altered cell morphology in NIH3T3 cells transfected with INTRA.

Alternatively, INTRA activity is measured by binding of INTRA to radiolabeled formin polypeptides containing the proline-rich region that specifically binds to SH3 containing proteins

(Chan, D.C. et al. (1996) EMBO J. 15: 1045-54). Samples of INTRA are run on SDS-PAGE gels, and transferred onto nitrocellulose by electroblotting. The blots are blocked for 1 hr at room temperature in TBST (137 mM NaCl, 2.7 mM KCl, 25 mM Tris (pH 8.0) and 0.1% Tween-20) containing non-fat dry milk. Blots are then incubated with TBST containing the radioactive formin
5 polypeptide for 4 hrs to overnight. After washing the blots four times with TBST, the blots are exposed to autoradiographic film. Radioactivity is quantitated by cutting out the radioactive spots and counting them in a radioisotope counter. The amount of radioactivity recovered is proportional to the activity of INTRA in the assay.

Alternatively, INTRA activity is demonstrated by measuring the binding of INTRA to Ca^{2+} using a Ca^{2+} overlay system (Weis, K. et al. (1994) J. Biol. Chem. 269:19142-19150). Purified
10 INTRA is transferred and immobilized onto a nitrocellulose membrane. The membrane is washed three times with buffer (60 mM KCl, 5 mM MgCl_2 , 10 mM imidazole-HCl, pH 6.8) and incubated in this buffer for 10 minutes with 1 μCi [$^{45}\text{Ca}^{2+}$] (NEN-DuPont, Boston, MA). Unbound [$^{45}\text{Ca}^{2+}$] is removed from the membrane by washing with water, and the membrane is dried. Membrane-bound
15 [$^{45}\text{Ca}^{2+}$] is detected by autoradiography and quantified using image analysis systems and software. INTRA activity is proportional to the amount of [$^{45}\text{Ca}^{2+}$] detected on the membrane.

Alternatively, INTRA activity is assayed by measuring the conversion of ^3H -cAMP to ^3H -adenosine in the presence of INTRA and 5' nucleotidase. INTRA is added to a solution containing 50 mM Tris-HCl pH 7.5, 10 mM MgCl_2 , 0.1 unit 5' nucleotidase (from *Crotalus atrox* venom), and
20 0.0064-2.0 μM ^3H -cAMP and the reaction is incubated at 37°C for a time period that would yield less than 15% cAMP hydrolysis in order to avoid non-linearity associated with product inhibition. Soluble radioactivity associated with ^3H -adenosine is quantitated using a Beta scintillation counter. The amount of radioactivity recovered is proportional to the activity of INTRA in the reaction.

25 XII. Functional Assays

INTRA function is assessed by expressing the sequences encoding INTRA at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which
30 contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the
35 recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP;

Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events

5 include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of

10 fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of INTRA on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding INTRA and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions

15 of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding INTRA and other genes of interest can be analyzed by northern analysis or microarray techniques.

20 **XIII. Production of INTRA Specific Antibodies**

INTRA substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the INTRA amino acid sequence is analyzed using LASERGENE software

25 (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A

30 peptide synthesizer (PE Biosystems) using FMOC chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for anti-peptide and anti-INTRA activity by, for example, binding the peptide or INTRA to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

35

XIV. Purification of Naturally Occurring INTRA Using Specific Antibodies

Naturally occurring or recombinant INTRA is substantially purified by immunoaffinity chromatography using antibodies specific for INTRA. An immunoaffinity column is constructed by covalently coupling anti-INTRA antibody to an activated chromatographic resin, such as

- 5 CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing INTRA are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of INTRA (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt

- 10 antibody/INTRA binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and INTRA is collected.

XV. Identification of Molecules Which Interact with INTRA

INTRA, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) Candidate molecules

15 previously arrayed in the wells of a multi-well plate are incubated with the labeled INTRA, washed, and any wells with labeled INTRA complex are assayed. Data obtained using different concentrations of INTRA are used to calculate values for the number, affinity, and association of INTRA with the candidate molecules.

- Alternatively, molecules interacting with INTRA are analyzed using the yeast two-hybrid
- 20 system as described in Fields, S. and O. Song (1989, *Nature* 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

INTRA may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S.

- 25 Patent No. 6,057,101).

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific

30 embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	53	129042	TESTNOT01	129042H1 (TESTNOT01), 129042T6 (TESTNOT01), 594163H1 (BRAVUNT02), 1376353T6 (LUNGNOT10), 1968641R6 (BRSTNOT04), 4193335F6 (BRAPDIT01), 5636985H1 (UTRSTMR01)
2	54	778003	COLNNOT05	778003H1 (COLNNOT05), 778003X29 (COLNNOT05), 793138X17 (PROSTUT03), 5533562H1 (HEARFET05)
3	55	1418671	KIDNNOT09	458013F1 (KERANOT01), 461367R6 (KERANOT01), 1418671H1 (KIDNNOT09), 1418671X301D1 (KIDNNOT09), 1452670F1 (PENITUT01), 1455886F1 (COLNFET02), 2921431H1 (SININOT04)
4	56	1456841	COLNFET02	214180X3 (STOMNOT01), 1456841H1 (COLNFET02), 1517021F1 (PANCTUT01), 2280709F6 (COLSUCT01), SBFA01757F1, SBFA04860F1, SBFA03431F1
5	57	2020010	CONNNOT01	520251R1 (MMLR2DT01), 552501H1 (SCORNOT01), 1297508H1 (BRSTNOT07), 1417085H1 (BRAINOT12), 1455946F1 (COLNFET02), 1864670H1 (PROSNOT19), 1922941R6 (BRSTTUT01), 1922941T6 (BRSTTUT01), 1930785H1 (COLNTUT03), 2020010F6 (CONNNOT01), 2020010H1 (CONNNOT01), 2879789H1 (UTRSTUT05), 3324110H1 (PTHYNOT03), 3766286H1 (BRSTNOT24), 4305754H1 (TESTTUT03)
6	58	2149037	BRAINOT09	1382860F1 (BRAITUT08), 1709135F6 (PROSNOT16), 1758155R6 (PITUNOT03), 1861076F6 (PROSNOT19), 2149037H1 (BRAINOT09), 2149037X15F1 (BRAINOT09), 2280366H1 (PROSNON01), 2524642F6 (BRAITUT21), 2590271H1 (LUNGNOT22), 2970418H2 (HEAONOT02), 3084127H1 (BRAIFET01), 4789892T6 (EPIBUNT01)
7	59	2162179	ENDCNOT02	2162179F6 (ENDCNOT02), 2162179H1 (ENDCNOT02), 3865236H1 (BRAITUT07)
8	60	2244706	HIPONON02	2244706H1 (HIPONON02), 3272168F6 (BRAINOT20), SBWA00950V1, SBWA03641V1, SBWA02322V1

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
9	61	2315805	OVARNOT02	363271R6 (PROSNOT01), 855363H1 (NGANNOT01), 1209030T1 (BRSTNOT02), 1265148R1 (SYNORAT05), 1294807F1 (PGANNOT03), 1351585F1 (LATRTUT02), 1852006F6 (LUNGFET03), 2316805H1 (OVARNOT02), 2320867H1 (OVARNOT02), 3563231F6 (SKINNOT05) 448783H1 (TYMNOT02), 470134R1 (MMLRIDT01), 720124F1 (SYNOOAT01), 1873477F6 (LEUKNOT02), 2320010H1 (OVARNOT02), 3049510T6 (LUNGNOT25), 3087109F6 (HEAONOT03), 4144881H1 (SINITUT04), 5089346H1 (UTRSTMR01)
10	62	2320010	OVARNOT02	214410F1 (STOMNOT01), 927356R1 (BRAINOT04), 2564901H1 (ADRETUT01)
11	63	2564901	ADRETUT01	1445950F6 (PLACNOT02), 2615168H1 (GBLANOT01), 2746963F6 (LUNGTUT11), 2746963T6 (LUNGTUT11), 3250984H1 (SEMVNOT03), 3459378H1 (293TF1T01), 3831615H1 (PANCNOT17), 4334378H1 (KIDCTMT01), 4818908H1 (PROSTUT17)
13	65	2658329	LUNGTUT09	1210539H1 (BRSTNOT02), 1210539R6 (BRSTNOT02), 1985147R6.comp (LUNGAST01), 2311120R6 (NGANNOT01), 2658329H1 (LUNGTUT09), 2717243F6 (THYRNOT09), 2831384F7 (TYMNOT03), 3846358H1 (DENDNOT01), 4898171H1 (OVARIDIT01)
14	66	2708944	PONSAZT01	309840R6 (TMLR2DT01), 1241166R6 (LUNGNOT03), 1381850H1 (BRAITUT08), 2194624F6 (THYRTUT03), 2212407F6 (SINTFET03), 2708944F6 (PONSAZT01), 2708944H1 (PONSAZT01), 4895659H1 (LIVRTUT12)
15	67	3315012	293TF1T01	532568R6 (BRAINOT03), 1300242F1 (BRSTNOT07), 1329265F1 (PANCNOT07), 1439786H1 (PANCNOT08), 2327916X23C1 (COLNNOT11), 2381037X37C1 (ISLTNOT01), 2381037X39C1 (ISLTNOT01), 3315012H1 (293TF1T01), SAEB00241R1
16	68	4155412	ADRENOT14	555524R6 (SCORNOT01), 4155412F6 (ADRENOT14), 4155412H1 (ADRENOT14), 4943387F6 (BRAIFEN05)

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
17	69	4831840	BRAVXTX03	286660H1 (EOSIHET02), 422026H1 (CARCTX01), 1734445F6 (COLNNOT22), 1734445T6 (COLNNOT22), 1970421F6 (UCMCL5T01), 2512308H1 (CONUTUT01), 4831840H1 (BRAVXTX03)
18	70	5676581	293TF2T01	702633R6 (SYNORAT03), 1000026R1 (BRSTNOT03), 2631308F6 (COLNTUT15), 3012653H1 (MUSCNOT07), 3252744H1 (OVRTUN01), 3315168H2 (293TF2T01), 3530354H1 (BLADNOT09), 4289137H1 (BRABDIR01), 4974749H1 (HELATX03), 5676581H1 (293TF2T01)
19	71	034159	THP1NOB01	034159H1 (THP1NOB01), 034159X305D3 (THP1NOB01), 406358R6 (EOSIHET02), 1974550F6 (UCMCL5T01), 3471911H1 (LUNGNOT27), 3522363H1 (ESOGTUN01), 4326520H1 (TLYMUNT01), SCJA01020V1, SCJA01764V1
20	72	129023	TESTNOT01	129023R6 (TESTNOT01), 775480R1 (COLNNOT05), 1649938F6 (PROSTUT09), 2518140F6 (BRAITUT21), 2688123H1 (LUNGNOT23), 4306520H1 (MONOTXT01)
21	73	1358940	LUNGNOT09	879273R1 (THYRNOT02), 967670T1 (BRSTNOT05), 1358940F6 (LUNGNOT09), 1358940H1 (LUNGNOT09), 1809259H1 (PROSTUT12), 1818790F6 (PROSNOT20), 1886716F6 (BLADTUT07), 1905126F6 (OVARNOT07), 3508881H1 (CONCNOT01), 3687018F6 (HEAANOT01), 3812474F6 (TONSNOT03)
22	74	1682320	PROSNOT15	1214001T1 (BRSTTUT01), 1259957F1 (MENITUT03), 1375132H1 (LUNGNOT10), 1682320H1 (PROSNOT15), 3137047H1 (SMCCNOT01), 3805984H1 (BLADTUT03), 3806302H1 (BLADTUT03)
23	75	1728263	PROSNOT14	1269315H1 (BRAINOT09), 1453910F1 (PENITUT01), 1728263H1 (PROSNOT14), g2115530
24	76	1867626	SKINBIT01	667711T6 (SCORNOT01), SXA01116V1, SXA01833V1, SXA02442V1

Table 1 (cont.)

25	77	1990126	CORPNOT02	426763T6 (BLADNOT01), 1647316F6 (PROSTUT09), 1757430R6 (PITUNOT03), 1830621F6 (THP1AZT01), 1990126H1 (CORPNOT02), 3250740H1 (SEMYNOT03)
26	78	2104180	BRAITUT02	1350750F1 (LATRTUT02), 1502445F1 (BRAITUT07), 1519125X301D1 (BLADTUT04), 2104180H1 (BRAITUT02), 2733677H1 (OVARTUT04)
27	79	2122241	BRSTNOT07	1402761H1 (LATRTUT02), 1402761T6 (LATRTUT02), 2122241F6 (BRSTNOT07), 2122241H1 (BRSTNOT07), 4989861H1 (LIVRTUT11)
28	80	2580428	KIDNTUT13	157262F1 (THP1PLB02), 1914234X29C1 (PROSTUT04), 1914467X12C1 (PROSTUT04), 1914467X13C1 (PROSTUT04), 1915166X14C1 (PROSTUT04), 2580428H1 (KIDNTUT13), SBKA01222F1
29	81	3397189	UTRSNOT16	759108R6 (BRAITUT02), 1911587T6 (CONNTUT01), 3397189H1 (UTRSNOT16)
30	82	4881249	UTRMTMT01	080470R1 (SYNORAB01), 998242R6 (KIDNTUT01), 4549519H1 (HELAUNT01), 4881249H1 (UTRMTMT01), SXAEO1512V1, SXAE02289V1, SXAE00433V1
31	83	431871	EOSINOT03	431871H1 (BRAVUNT02), 460185R1 (KERANOT01), 636514F1 (NEUTGMT01), 1975990T6 (PANCUTUT02), 2212046H1 (SINTFET03), 2257310R6 (OVARTUT01), 2300180R6 (BRSTNOT05), 4884920F6 (LUNLTMT01), SCEA00887V1
32	84	526155	EOSINOT02	526155H1 (EOSINOT02), 794168R6 (OVARNOT03), 1260927R1 (SYNORAT05), 1975556F6 (PANCUTUT02), 5157385H1 (BRSTTMT02)
33	85	676234	CRBLNOT01	676234H1 (CRBLNOT01), 2241232F6 (PANCUTUT02), 2241232T6 (PANCUTUT02), 2824092H1 (ADRETUT06), 4248435T6 (BRABDIT01)
34	86	720145	SYNOOAT01	433978H1 (THYRNOT01), 720145H1 (SYNOOAT01), 720145R6 (SYNOOAT01), 2107540T6 (BRAITUT03), 4722278H1 (COLCTUT02)
35	87	1001951	BRSTNOT03	1001951H1 (BRSTNOT03), 1001951R6 (BRSTNOT03), SXYA00708V1, SXYA01879V1, SXYA00520V1, SXYA00731V1, SXYA00926V1
36	88	1243349	LUNGNOT03	050083X316F1 (CHAONOT01), 050083X326F1 (CHAONOT01), 050083X346F1 (CHAONOT01), 050083X350F1 (CHAONOT01), 1243349H1 (LUNGNOT03), 2751089R6 (THP1AZS08), 3773254F6 (BRSTNOT25), 3997530H1 (PROSBPS05), g844357, g1940784, g4539083

Table 1 (cont.)

37	89	1338201	COLNNOT13	256461H1 (HNT2RAT01), 1338201H1 (COLNNOT13), 1338201X12 (COLNNOT13), 1338201X18 (COLNNOT13), 1338201X21 (COLNNOT13), 2078127H1 (ISLTNOT01), 9777838, q1146680, q1406379
38	90	1405141	LATRUT02	189682R6 (CARDNOT01), 551762R6 (SCORNOT01), 1405141X302D1 (LATRTUT02), 1459886X16C1 (COLNFET02), 2601416H1 (UTRSNOT10), 2836108H2 (LYMNUT03), 3031895F6 (LYMNUT05), 3127628H1 (LUNGUTUT12), 3402733H1 (ESOGNOT03), 4289784F6 (BRABDIR01), 4339406H1 (BRAUNOT02), 4712515H1 (BRAIHCT01), 4746879H2 (SMCRUNT01), 5091792F6 (UTRSTMR01), 5679882H1 (BRAENOT02), 5927661H1 (BRAIFET02)
39	91	1686305	PROSNOT15	499154R6 (NEUTLPT01), 1686305F6 (PROSNOT15), 1686305H1 (PROSNOT15), 2306450R6 (NGANNOT01), 2446232F6 (THP1NOT03), 2446232T6 (THP1NOT03), 3050482H1 (LUNGNOT25), 3694303F6 (LUNGNOT35), 3825239H1 (BRAIHCT01), 3931022H1 (PROSTUT09), 4383527H1 (BRAVUTT02)
40	92	1688972	PROSTUT10	878019H1 (LUNGAST01), 1255436F2 (MENITUT03), 1330287F1 (PANCNOT07), 1400064F6 (BRAITUT08), 1688972H1 (PROSTUT10), 2018742F6 (THP1NOT01), 2047754X12F1 (SININOT01), 3002925H1 (TYLMNOT06), 3744192H1 (THYMNUT08)
41	93	1812494	PROSTUT12	1322590F6 (BLADNOT04), 1684555F6 (PROSNOT15), 2120930H1 (BRSTNOT07), 2266093H1 (UTRSNOT02), 2631470F6 (COLNTUT15), 3980110H1 (LUNGUTUT08), 5115462H1 (ENDITXT01), SADA00912R1
42	94	2013853	TESTNOT03	2013853H1 (TESTNOT03), 2013853R6 (TESTNOT03), SXBC01227V1, SCSA04222V1
43	95	2284925	BRAINON01	464655X11 (LATRNOT01), 464655X12 (LATRNOT01), 464655X28 (LATRNOT01), 482019X21 (HNT2RAT01), 1443611R1 (THYRNUT03), 1443611X22 (THYRNUT03), 2284925H1 (BRAINON01), 2882173F6 (UTRSTUT05), 3485205F6 (KIDNNOT31), 3485205T6 (KIDNNOT31), SAAB00144R1

Table 1 (cont.)

44	96	2376728	ISLTNOT01	413593R6 (BRSTNOT01), 823803R1 (PROSNOT06), 860037R1 (BRAITUT03), 1282102F1 (COLNNOT16), 1733518F6 (BRSTTUT08), 2376728F6 (ISLTNOT01), 2376728H1 (ISLTNOT01), 2937285F6 (THYMFET02), 3108296H1 (BRSTTUT15), 3212546H1 (BLADNOT08), 3462704H1 (293TF2T01)
45	97	2790762	COLNTUT16	126628F1 (LUNGNOT01), 126628R1 (LUNGNOT01), 2790762F6 (COLNTUT16), 2790762H1 (COLNTUT16), 4002872H1 (HNT2AZS07), 9678705
46	98	2869164	THYRNOT10	1607765F6 (LUNGNOT15), 2869164F6 (THYRNOT10), 2869164H1 (THYRNOT10), 2869164T6 (THYRNOT10), 2890205H1 (LUNGFET04), 2891521F6 (LUNGFET04), 3094580X305D1 (CERVNOT03)
47	99	3317629	PROSBPT03	3166243H1 (SATABT007), 3317629F6 (PROSBPT03), 3421114X302F1 (UCMCNOT04), 4635773F6 (MYEPTXT01), 4635773T6 (MYEPTXT01)
48	100	3870488	BMARNOT03	1670688F6 (BMARNOT03), 3039406T6 (BRSTNOT16), 3870488H1 (BMARNOT03), 4773630H1 (BRAONOT01)
49	101	3886318	UTRSNOT05	198182F1 (KIDNNOT02), 474711R1 (MMLR1DT01), 733227R1 (LUNGNOT03), 1236870F1 (LUNGFET03), 1502818F1 (BRAITUT07), 3742588H1 (THYMNOT08)
50	102	4043934	LUNGNOT35	4043934F6 (LUNGNOT35), 4043934H1 (LUNGNOT35), 91664159, 92114678, 93665589
51	103	4371445	THYMNOT11	4371445F6 (THYMNOT11), 4371445H1 (THYMNOT11), 4371445T6 (THYMNOT11), 9691417
52	104	5527925	KIDNNOT34	878842R1 (THYRNOT02), 1662614F6 (BRSTNOT09), 1820183F6 (GELATUT01), 2275208H1 (PROSNON01), 2864564H1 (KIDNNOT20), 2890511H1 (LUNGFET04), 4312193H1 (BRAFNOT01), 5175111F6 (EP1BTXT01), 5876074H1 (BRAUNOT01)

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
1	446	T24 T144 S251 S384 S404 T114 T118 T121 T172 S181 S247 Y53 Y422	N117 N232	SH3 domain: E387-I441	g2232009, thyroid hormone responsive protein [Rattus norvegicus]. Shah, G.N. et al. (1997) Biochem. J. 327:617-23.	BLAST - GenBank BLAST - DOMO BLIMPS - BLOCKS BLIMPS - PRINTS HMMER - PFAM MOTIFS
2	340	T26 S51 T146 S211 S270 S308 S73 S277 S317 Y71		SH2 domain: W240-Y316	g3738265 SH2 domain- containing protein [Mus musculus]	BLAST - GenBank BLAST - DOMO BLIMPS - PRINTS HMMER - PFAM MOTIFS
3	353	T45 S232 T353 T78 S88 S163 S176 T222 S240 S284 S302 T326 S338 S116 S120 T154 S226 S295 S337		Pleckstrin homology domains: T247-T353 G4-H104 S120-K250	g5381422 pleckstrin 2 [Homo sapiens]	BLAST - GenBank BLAST - PRODOM HMMER - PFAM MOTIFS
4	593	S230 S415 T84 T115 S214 S231 S309 S355 S372 T377 T387 S529 S580 S5 T36 S41 S90 S205 T263 S264 T343 T371 S410 S445 S483 S528 T547	N19 N542	SH3 domain: L453-L507 EPS8 region - SH3/phosphorylation domain: S2-P395	g309217 Eps8 (EGF receptor kinase substrate) [Mus musculus]	BLAST - GenBank BLAST - PRODOM HMMER - PFAM MOTIFS

Table 2

5	358	T42 S82 T204 T233 S261 T271 T279 S285 S330 S55 T102 S153 S254 S353	N338	Ankyrin repeat: G40-G67	g485107 similar to ankyrin repeat region [C. elegans]	BLAST - GenBank HMMER - PFAM MOTIFS
6	749	S137 T401 S406 T407 S580 T29 S140 S148 S149 S287 T336 S342 S360 S511 S551 T627 T29 S104 T368 S480 T616 Y141 Y303	N147 N392 N453 N640	Transmembrane domain: W280-I297 SH3 domain: R483-L537 Probable rabGAP domains: I159-P168 Y200-G205	g1519685 contains similarity to SH3 domains [C. elegans].	BLAST - GenBank BLIMPS - PRINTS BLIMPS - PFAM HMMER - PFAM HMMER MOTIFS
7	139	T51 T113 S106	N31		g169306 calmodulin [Phytophthora infestans]	BLAST - GenBank
8	539	S52 S84 T114 S186 S430 T468 S15 S110 S241 S307 S309 S353 S362 S363 S389 S485 S118 S169 S181 S210 T319 S385 T434 T523 Y208 Y305	N533	Pleckstrin homology domain: R192-A291	g4151807 membrane- associated guanylate kinase- interacting protein 2 (Maguin-2) [Rattus norvegicus]	BLAST - GenBank HMMER - PFAM MOTIFS
9	319	S169 S214 S233 S240 S150	N126	Tumor necrosis factor and nerve growth factor receptors - Conserved domain containing six cysteines: L166-C204	g2809400 Sprouty 2 (antagonist of FGF signaling) [Homo sapiens]	BLAST - GenBank HMMER - PFAM MOTIFS

Table 2 (cont.)

Polyptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
10	747	T194 T344 T561 S655 S45 T58 T60 T74 T81 T171 S287 T294 S446 T526 S608 T610 T733 S126 S133 T165 S170 T190 S234 T251 T429 S470 S492 T522 S546 S735 S741 Y504 Y543	N32 N54 N533 N642		g550420 trg (transcript negatively regulated by thyroid stimulating hormone) [Rattus norvegicus]	
11	266	S62 T76 T183 S222 S4 T5 S256 S260 Y179	N47	Diacylglycerol/phorbol ester binding domain: E177-N223		PROFILESCAN HMMER - PFAM MOTIFS
12	345	T87 S131 S213 T241 S299 S323 T34 T69 T223 S307	N40 N70	Annexin domain: G58-L110 L122-R143 I137-L182 L262-F316 E311-D326 A327-C340	g3688370, annexin 31 (annexin XXXI) [Homo sapiens]. Morgan, R.O. and Fernandez, M.P. (1998) FEBS Lett. 434:300-304.	BLAST - GenBank HMMER - PFAM BLIMPS - BLOCKS BLIMPS - PRINTS MOTIFS
13	437	S40 T66 T79 S93 T241 T289 S305 S342 T375 S47 S270 S362 T371 T393			g685183 NGD5 gene product (regulated by opioid treatment) [Murinae gen. sp.]	BLAST - GenBank MOTIFS

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
14	441	S333 S419 T10 T24 T322 S403 S407 S422 T453 S33 S270 S329 T352 S487		Ankyrin repeats: G46-N73 G80-D107	<u>g6460678</u> ankyrin-related protein [Deinococcus radiodurans].	BLAST - GenBank HMMER - PFAM MOTIFS
15	487	S31 T51 S62 T220 T237 T254 T427 S453 T471 S482 T483 T95 S182	N242 N481	Signal peptide: M1-A28 Histidine acid phosphatase domains: R88-T95 K311-W323 Acid phosphatase-like region: E75-S484	<u>g4105496</u> multiple inositol polyphosphate phosphatase [Mus musculus].	BLAST - GenBank BLAST - PRODOM BLIMPS - BLOCKS HMMER SPSCAN MOTIFS
16	282	S25 T125 T157 T203 S31 S46 S107 S133 S194 S218 S257	N17 N74 N216		<u>g688297</u> VDUP1 (1,25- dihydroxy- vitamin D-3 up- regulated polypeptide [Homo sapiens].	BLAST - GenBank MOTIFS
17	581	T147 T327 S477 S41 T119 T123 T129 T209 S232 S243 S257 S299 S341 S347 T366 S371 S142 S220 S223 S237 S276 S323 S399 T472 T487 S518	N221 N358		<u>g6013191</u> , activating signal cointegrator 1 [H. sapiens]. Kim, H.J. et al. (1999) Mol. Cell. Biol. 19:6323-6332.	BLAST - GenBank MOTIFS

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
18	530	S23 T46 S219 S221 T267 T268 S290 S303 T370 T382 S406 S446 T2 S31 S195 S339 S358 T375 S379 S399 T424 T445 T504	N43 N99	Signal peptide: M1-S23 WW/rsp5/WWP repeat domain: E123-P153 Trehalase domains: P80-T90 E129-N142	g1255031 FBP 30 (formin binding protein 30) [Mus musculus]	BLAST - GenBank SPSCAN HMMER - PFAM BLIMPS - BLOCKS MOTIFS
19 (034159)	475	S264 T5 T9 S33 S163 S171 S211 S217 S241 T267 S343 S370 T386 S472 S16 S110 S111 S151 S152 S246 T260 S264 T405	N15 N62 N101 N291 N384 N443	Pleckstrin M79-D189 GTPase activator K248- A459	g35013 n-chimaerin	Motifs BLAST_GENBANK HMMER_PFAM BLIMPS_PRINTS BLIMPS_PFAM BLAST_PRODOME BLAST_DOMO
20 (129023)	368	S8 S54 S70 S99 T158 S159 S253 S361 S30 T152 S308	N24 N68 N359	Signal peptide: M1-Q25 WW (signal transduction associated) domain: Y61-P75		Motifs SPSCAN BLIMPS_PRINTS
21 (1358940)	476	S104 S182 T343 S122 T148 T157 T197 S205 T360 S429 T467 T133 T269 T292 T323 S339		EF-hand Calcium binding domain: D231- D421	g3297882 atopy-related autoantigen CALC [H. sapiens].	Motifs BLAST_GENBANK HMMER_PFAM BLAST_PRODOME

Table 2 (cont.)

22 (1682320)	171	T70 T151 S97 Y11 Y24		Leucine zipper: L38- L59 Peptidyl-Prolyl Cis- Trans Isomerase CYP6: L59-F170	g1354207 rofl FK506 binding protein	Motifs BLAST_GENBANK BLAST_PRODOM BLAST_DOMO
23 (1728263)	163	S16 S39 S56 T101 T112 T131 S148 Y92	N70	EF-hand calcium binding domain: D140- F152	g21209 caltractin [Scherffelia dubia]	Motifs BLAST_GENBANK BLAST_PRODOM
24 (1867626)	354	T230 T148 T252 S306 S315 T328 S8 T20 T27 S40 S71 T189 T244 T259 T288	N58 N64 N146 N250	Leucine zipper: L326- L347 ATP-Binding motif: E93-E320 Vasodilator-Stimulated Actin-Binding Phosphoprotein motif: M1-A109	g3834607 homer-1b [Mus musculus]	Motifs BLAST_GENBANK BLAST_PRODOM
25 (1990126)	365	T36 S47 S191 T198 S200 T359 T56 T124 S307 Y80 Y155	N189 N264 N297 N320	Src homology domain 3: R308-L364	g1407657 endophilin II	Motifs BLAST_GENBANK HMMER_PFAM BLIMPS_PRINTS BLAST_DOMO
26 (2104180)	274	T71 S126 T137 S230 S251 T7 S141 S155 Y152	N56	Protein Kinase C2 domain: L55-H135	g3876326 similar to protein kinase C2	Motifs BLAST_GENBANK HMMER_PFAM
27 (2122241)	129	T11 S24 S58 T100 S112 T89		Nascent polypeptide- associated complex alpha chain: G39-T128		Motifs BLAST_DOMO
28 (2580428)	626	S84 S93 S192 S278 T411 S10 S18 T114 S302 S482	N293 N577 N599	Interferon-gamma inducible protein motif: M1-M115, C522- A574	g4886493 and g6942315, [H. sapiens].	Motifs BLAST_PRODOM

Table 2 (cont.)

29 (3397189)	157	S7	N97	Signal peptide: M1-S29 Glycosyl hydrolase: L62-L137 Beta D Galactosidase: R28-L153	g2547317 lysosomal beta- galactosidase W09914328	Motifs BLAST_GENBANK SPSCAN HMMER BLIMPS_BLOCKS BLAST_PRODOR
30 (4881249)	383	T7 T26 S90 T62 T81 S102 T363 S3 T210 T256 T286 Y158	N70 N190 N223 N289	WVP (Signal transduction associated proline binding domain):L201- P230	g5059333 ubiquitin ligase	Motifs BLAST_GENBANK HMMER_PFAM BLIMPS_PRINTS
31	478	S186 S202 S270 S354 S455 S9 S94 T175		Signal peptide: M1-A64 Ankyrin repeat: D36-E63 Ankyrin repeat protein domain: Q111-Y174; C285-V447	g1204166 , hypothetical Ank-repeat/BTB- domain protein [Schizosaccharo myces pombe].	MOTIFS SPSCAN HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-PRODOR
32	275	S259 T74 T173 S186 T231 S21 T63 T219 S255 S267			COP9 complex subunit 7b [Mus musculus] g3309176	BLAST-Genbank MOTIFS
33	217	T4 T106 S209		Signal peptide: M1-C25 Transmembrane domains: A82-T100; R116-I34 Claudin signature: T21-W30; G49-V55 Q63-L73; D146-V152	claudin-9 protein [Mus musculus] g4325296	BLAST-Genbank MOTIFS SPSCAN HMMER BLIMPS-PRINTS

Table 2 (cont.)

34	74	S6 T58 S54		TPR domain: Y18-P46			MOTIFS HMMER-PFAM BLIMPS-PRODOM
35	367	S309 S24	N240	Transmembrane domain: L257-T277 Armadillo/beta-catenin repeat: 219-252; L252-L265			MOTIFS HMMER BLIMPS-PFAM
36	1113	T17 S43 S609 T755 T52 T215 S239 S287 T307 T313 S504 S510 S535 T536 S635 S688 S804 S812 T856 S863 T884 S938 T983 S996 S1004 S5 T196 S353 S433 T550 S592 S593 S727 T748 S762 S839 T928 S944 T952 T968 S1074 Y23 Y134	N175 N323 N365 N633 N724	PDZ domains: V53-E135; E152-D237 L252-H335; E472-D560 H573-D657; T673-Q754 K989-N1070 SH3 domain repeat: G98-K111 SH3 domain protein signature: V153-G249 GLGF domain: L676-K752	AMPA receptor interacting protein GRIP [Rattus norvegicus] g1890856		BLAST-Genbank MOTIFS HMMER-PFAM BLIMPS-PFAM BLIMPS-PRODOM BLAST-PRODOM BLAST-DOMO
37	511	S147 S88 S136 T228 T320 S467 T15 T81 T118 T168 S281 S289 S311 S354 S455 T461 T480 T494 Y16 Y114	N86 N116 N315 N316 N355 N403 N425 N429 N478	SH3 domain: Q342-L400	g6563258, insulin receptor tyrosine kinase substrate [Homo sapiens].		BLAST-Genbank MOTIFS HMMER-PFAM

Table 2 (cont.)

38	1177	S421 T936 T96 T121 S164 S209 T256 S277 S325 S374 S388 T397 S435 S443 T456 T519 S662 T669 S727 T901 S983 S1114 S14 T70 S307 S331 S416 S545 T565 S609 T626 T703 S804 S845 S853 S867 T921 S972 T1021 S1108 Y214 Y879 Y171	N84 N1112	Armadillo beta-catenin repeat: I196-L205	trg [Rattus norvegicus] g550420	BLAST-Genbank MOTIFS BLIMPS-PFAM
39	665	S245 T358 S480 T76 S110 S119 S121 T266 S284 S481 S521 S561 S632 S654 S655 S72 S73 S130 T171 S205 T411 S428 T475 S476 T491 S513 S523 T634 Y165 Y567 Y578	N197 N479	TPR domains: L136-P164; Y204-P232 E285-G313; P319-G347 F353-P381 TPR repeat: K137-E252; K286-K395	g6272680, TPR- containing protein involved in spermatogenesis TPIS [Mus musculus]. Takaishi, M. and Huh, N.H. (1999) Biochem. Biophys. Res. Commun. 264:81-85.	BLAST-Genbank MOTIFS HMME-PFAM BLIMPS-PRODOM BLAST-DOMO
40	125	T119 T67		Signal peptide: M1-A53 SH3 domain: R68-L124 R68-A78; K112-L124		MOTIFS HMME-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS

Table 2 (cont.)

Poly-peptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
41	366	S43 S45 T102 S157 T202 T220 S293 S219 T256 T325 S350 Y237		Signal peptide: M1-S30 Ankyrin repeat: G174-S206	g289693, homology with isopentenyl- diphosphate- delta-isomerase; [C. elegans]. Sulston, J. et al. (1992) Nature 356:37-41.	MOTIFS SPSCAN HMMER-PFAM BLIMPS-PFAM
42	173	S16 S42 S48 T67 S100 S111 S152 S86	N126	EF Hands: E22-R53; L57-F85 K94-M122; L135-L163 S-100/IcaBP type calcium binding protein signature: L6-E57; L132-K168 Recoverin family signature: V61-T82; S86-D105 Calmodulin repeat: R25-I79; L119-S157	calcineurin B- like protein (CBLP) [Rattus norvegicus] g220688	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS PROFILES-SCAN BLAST-DOMO
43	761	S227 S293 S393 S19 S43 T149 T161 S277 T346 T370 T415 T529 T572 S630 T683 S711 T746 S74 S196 S252 S283 S300 T444 T472 T591 S754 Y589	N117 N467 N492 N555	3',5'-cyclic nucleotide phosphodiesterase domain: Y490-H729 D418-W744 3',5'-cyclic nucleotide phosphodiesterase signature: L2-H56; L449-H485 Y490- H501; L516-D556 T572-E610; D657-S711	CAMP-specific cyclic nucleotide phosphodiesterase PDE8 [Mus musculus].	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS PROFILES-SCAN BLAST-PRODOM BLAST-DOMO

Table 2 (cont.)

Poly-peptide SEQ ID NO.	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
44	249	S16 S89 T115 S212 S239 T12 T117 S137 S187 S197 S230 Y208	N84	Pleckstrin homology domain: V35-T131 Rho-GEF domain: L36-C178; E118-D245 FYVE zinc finger: N59-Y64; R171-C183 R202-S212	g3292902, PUTATIVE RHO/RAC GUANINE NUCLEOTIDE EXCHANGE FACTOR [H. sapiens].	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-PFAM BLAST-PRODOM
45	247	S109 S44 S53 S123 T138 S167 S95 T98 S127 T220	N90		putative phosphatidyl- inositol 3-kinase [Carassius auratus] g4001815	BLAST-GenBank MOTIFS
46	316	S313 S201 T223 T262 Y186 Y270			g3811347, cytosolic phospholipase A2 beta [Homo sapiens].	BLAST-GenBank MOTIFS
47	334	T119 S97 T182 T244 S316 S317 S324 S60 T72 S97 T179 S187 S290 Y52 Y323	N58 N322	Fes/CIP4 homology domain: G8-L98 SH3 domain/division control protein signature: F6-F287	macrophage actin- associated- tyrosine- phosphorylated protein [Mus musculus] g3947712	BLAST-GenBank MOTIFS HMMER-PFAM BLAST-PRODOM
48	113	T65 S66 T43		SH3 domain: K34-L90	SLP-76 associated protein (TCR- stimulated PK substrate) [Homo sapiens] g2072873	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-PRINTS

Table 2 (cont.)

Poly-peptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
49	264	S18 T76 T163 S181 S167 S223		Wilm's tumor protein signature: D97-P111	SH3 domain binding protein [Rattus norvegicus] g1185397 (P-value= 4.6x10- 8).	BLAST-GenBank MOTIFS BLIMPS-PRINTS
50	185	T24 S81 S149 S151 S160 S162 S75 S99 S177 Y176		EF-hands: K101-L129; L143-S171 Recoverin family signature: I23-G42; S93-N112 Calcium binding protein signature: E12-Y104	g1848271, Calcium and integrin binding protein CIB [Homo sapiens]	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-PRODOM
51	72	T18 S25 T20		Synapse-associated SH3 domain protein signature: M13-E67	homolog of Drosophila discs large protein isoform 1 [Homo sapiens] g558438 (P-value= 7.9x10- 9).	BLAST-GenBank MOTIFS BLAST-PRODOM
52	434	S123 T128 S418 S94 T105 S159 S205 T291 S308 S314 T326 T358 S383 S406 S84 T128 T212 Y220	N216 N231	Signal peptide: M1-A50 EF hand: I366-R394 Recoverin family signature: V370-L391	similar to EF hand [C. elegans] g3875264.	BLAST-GenBank MOTIFS SPSCAN HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
53	543-587	Reproductive (0.211) Developmental (0.158) Nervous (0.158)	Cancer (0.421) Cell Proliferation (0.263) Inflammation (0.211)	PBLUESCRIPT
54	273-317 651-695	Nervous (0.462) Gastrointestinal (0.385) Cardiovascular (0.077) Developmental (0.077)	Cancer (0.538) Cell Proliferation (0.308) Inflammation (0.154)	PSPORT1
55	110-154	Developmental (0.174) Gastrointestinal (0.174) Reproductive (0.174)	Cell Proliferation (0.435) Cancer (0.261) Inflammation (0.174)	pINCY
56	273-317 1461-1505	Gastrointestinal (0.821) Reproductive (0.143) Developmental (0.036)	Cancer (0.607) Inflammation (0.286) Cell Proliferation (0.036)	pINCY
57	595-639	Reproductive (0.313) Nervous (0.217) Hematopoietic/Immune (0.120)	Cancer (0.482) Inflammation (0.217) Cell Proliferation (0.169)	pINCY
58	703-747 1297-1341	Reproductive (0.250) Nervous (0.205) Gastrointestinal (0.125)	Cancer (0.509) Cell Proliferation (0.196) Inflammation (0.196)	pINCY
59	417-461	Nervous (0.300) Cardiovascular (0.200) Reproductive (0.200)	Inflammation (0.300) Trauma (0.300) Cancer (0.200) Cell Proliferation (0.200)	pINCY
60	1189-1233	Nervous (1.000)	Neurological (0.500) Trauma (0.333)	PSPORT1
61	272-316	Reproductive (0.314) Gastrointestinal (0.186) Nervous (0.157)	Cancer (0.529) Inflammation (0.200) Cell Proliferation (0.129)	PSPORT1
62	273-317 2055-2099	Hematopoietic/Immune (0.333) Reproductive (0.238) Gastrointestinal (0.167)	Inflammation (0.452) Cancer (0.333) Trauma (0.143)	PSPORT1
63	1-34	Reproductive (0.256) Nervous (0.188) Gastrointestinal (0.120)	Cancer (0.504) Inflammation (0.203) Cell Proliferation (0.195)	PSPORT1

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
64	489-533	Reproductive (0.312) Gastrointestinal (0.125) Nervous (0.125)	Cancer (0.438) Cell Proliferation (0.375) Inflammation (0.188)	pINCY
65	273-317	Reproductive (0.265) Nervous (0.224) Developmental (0.102)	Cancer (0.469) Cell Proliferation (0.286) Inflammation (0.204)	pINCY
66	1028-1072	Cardiovascular (0.286) Nervous (0.200) Reproductive (0.200)	Cancer (0.429) Cell Proliferation (0.171) Inflammation (0.171)	pINCY
67	325-369	Reproductive (0.222) Nervous (0.194) Cardiovascular (0.167) Gastrointestinal (0.167)	Cancer (0.472) Cell Proliferation (0.333) Inflammation (0.139)	pINCY
68	921-965	Endocrine (0.250) Musculoskeletal (0.250) Reproductive (0.250) Urologic (0.250)	Cancer (0.750) Trauma (0.250)	pINCY
69	1029-1073	Reproductive (0.216) Gastrointestinal (0.176) Hematopoietic/Immune (0.157)	Cancer (0.510) Inflammation (0.275) Cell Proliferation (0.118)	pINCY
70	1405-1449	Hematopoietic/Immune (0.200) Nervous (0.200) Gastrointestinal (0.160) Reproductive (0.160)	Cancer (0.360) Inflammation (0.360) Cell Proliferation (0.200)	pINCY
71	280-324	Hematopoietic/Immune (0.500) Gastrointestinal (0.092) Reproductive (0.092)	Cancer (0.364) Inflammation (0.295) Cell proliferation (0.205)	pBLUESCRIPT
72	380-424	Reproductive (0.227) Gastrointestinal (0.205) Cardiovascular (0.114)	Cancer (0.455) Inflammation (0.364) Trauma (0.045)	pBLUESCRIPT

Table 3 (cont.)

73	433-477	Nervous (0.241) Reproductive (0.231) Gastrointestinal (0.130)	Cancer (0.398) Inflammation (0.333)	pINCY
74	786-830	Reproductive (0.342) Nervous (0.210)	Cancer (0.474) Cell proliferation (0.184) Inflammation (0.105)	pINCY
75	1-47	Gastrointestinal (0.286) Reproductive (0.286) Developmental (0.143) Hematopoietic/Immune (0.143)	Cancer (0.571) Cell proliferation (0.286) Inflammation (0.143)	pINCY
76	380-424	Nervous (0.300) Reproductive (0.200)	Inflammation (0.400) Cancer (0.200) Cell proliferation (0.200)	pINCY
77	30-74	Gastrointestinal (0.222) Reproductive (0.222) Cardiovascular (0.153) Nervous (0.153)	Inflammation (0.375) Cancer (0.361) Cell proliferation (0.139)	pINCY
78	487-531	Nervous (0.300) Reproductive (0.183) Cardiovascular (0.117)	Cancer (0.433) Inflammation (0.200) Neurological (0.133)	pSPORT1
79	595-639	Reproductive (0.305) Nervous (0.179)	Cancer (0.526) Inflammation (0.326) Cell proliferation (0.179)	pINCY
80	109-153	Gastrointestinal (0.126) Reproductive (0.235) Hematopoietic/Immune (0.216) Nervous (0.157)	Cancer (0.529) Inflammation (0.255)	pINCY
81	109-153	Gastrointestinal (0.286) Musculoskeletal (0.286) Reproductive (0.286)	Cancer (0.571) Inflammation (0.286)	pINCY
82	163-207	Reproductive (0.424) Gastrointestinal (0.152) Nervous (0.121)	Cancer (0.424) Inflammation (0.242) Cell proliferation (0.182)	pINCY
83	496-540	Reproductive (0.242) Nervous (0.182) Hematopoietic/Immune (0.167)	Cancer (0.455) Inflammation/Trauma (0.364) Cell Proliferation (0.152)	pSPORT1
84	1022-1066	Reproductive (0.248) Nervous (0.208) Cardiovascular (0.136)	Cancer (0.464) Inflammation/Trauma (0.304) Cell Proliferation (0.184)	pSPORT1

Table 3 (cont.)

85	39-83	Nervous (0.286) Endocrine (0.143) Gastrointestinal (0.143) Hematopoietic/Immune (0.143) Reproductive (0.143)	Cancer (0.571) Inflammation/Trauma (0.286) Neurological (0.143)	PSPORT1
86	471-515	Hematopoietic/Immune (0.167) Musculoskeletal (0.167) Reproductive (0.167)	Cancer (0.556) Cell Proliferation (0.167) Inflammation/Trauma (0.167)	PSPORT1
87	595-639 982-1026	Reproductive (0.294) Cardiovascular (0.176) Gastrointestinal (0.176)	Cancer (0.706) Inflammation/Trauma (0.294) Cell Proliferation (0.118)	PSPORT1
88	1101-1163	Reproductive (0.625) Gastrointestinal (0.250) Cardiovascular (0.125)	Cancer (0.750) Inflammation/Trauma (0.250)	PSPORT1
89	1245-1289	Gastrointestinal (0.387) Reproductive (0.355) Cardiovascular (0.065)	Cancer (0.548) Inflammation/Trauma (0.323) Cell Proliferation (0.161)	pINCY
90	3720-3764	Nervous (0.328) Gastrointestinal (0.121) Reproductive (0.121)	Cancer (0.397) Inflammation/Trauma (0.310) Cell Proliferation (0.155)	pINCY
91	659-703 1622-1666	Hematopoietic/Immune (0.273) Nervous (0.182) Cardiovascular (0.121) Reproductive (0.121)	Cancer (0.455) Cell Proliferation (0.333) Inflammation/Trauma (0.303)	pINCY
92	104-148	Reproductive (0.310) Nervous (0.241) Developmental (0.138) Gastrointestinal (0.138)	Cancer (0.483) Inflammation/Trauma (0.241) Cell Proliferation (0.172)	pINCY
93	820-864	Reproductive (0.340) Cardiovascular (0.120) Nervous (0.120)	Inflammation/Trauma (0.440) Cancer (0.400) Cell Proliferation (0.160)	pINCY
94	504-554	Reproductive (1.000)	Inflammation/Trauma (1.000)	PBLUESCRIPT
95	198-242	Reproductive (0.424) Nervous (0.273)	Cancer (0.576) Inflammation/Trauma (0.182)	PSPORT1
96	307-351 712-756	Reproductive (0.412) Hematopoietic/Immune (0.137) Cardiovascular (0.118) Gastrointestinal (0.118)	Cancer (0.608) Inflammation/Trauma (0.275) Cell Proliferation (0.098)	pINCY

Table 3 (cont.)

97	433-477	Developmental (0.200) Reproductive (0.200) Cardiovascular (0.133) Gastrointestinal (0.133) Nervous (0.133)	Cell Proliferation (0.400) Cancer (0.333) Inflammation/Trauma (0.200)	pINCY
98	474-1018	Cardiovascular (0.190) Reproductive (0.190) Hematopoietic/Immune (0.143) Musculoskeletal (0.143)	Cancer (0.381) Inflammation/Trauma (0.333)	pINCY
99	422-466 998-1042	Hematopoietic/Immune (0.667) Reproductive (0.222) Developmental (0.111)	Inflammation/Trauma (0.556) Cancer (0.222) Cell Proliferation (0.222)	pINCY
100	444-488	Hematopoietic/Immune (0.455) Nervous (0.182) Cardiovascular (0.091)	Inflammation/Trauma (0.546) Cancer (0.182) Cell Proliferation (0.182)	pINCY
101	1578-1622	Reproductive (0.250) Nervous (0.170) Gastrointestinal (0.156)	Cancer (0.482) Inflammation/Trauma (0.345) Cell Proliferation (0.167)	pINCY
102	15-59	Cardiovascular (1.000)	Cancer (1.000)	pINCY
103	487-531	Hematopoietic/Immune (1.000)		pINCY
104	967-1011	Reproductive (0.235) Nervous (0.191) Gastrointestinal (0.147)	Cancer (0.515) Inflammation/Trauma (0.294) Cell Proliferation (0.118)	pINCY

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
53	TESTNOT01	The library was constructed using RNA isolated from the testicular tissue of a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
54	COLNNOT05	The library was constructed using RNA isolated from the sigmoid colon tissue of a 40-year-old Caucasian male during a partial colectomy. Pathology indicated Crohn's disease involving the proximal colon and including the cecum. The ascending and transverse colon displayed linear ulcerations and skip lesions. Transmural inflammation was present.
55	KIDNNOT09	The library was constructed using RNA isolated from the kidney tissue of a Caucasian male fetus who died at 23 weeks' gestation.
56	COLNFET02	The library was constructed using RNA isolated from the colon tissue of a Caucasian female fetus who died at 20 weeks' gestation.
57	CONNNOT01	The library was constructed using RNA isolated from mesentery fat tissue obtained from a 71-year-old Caucasian male during a partial colectomy and permanent colostomy. Family history included atherosclerotic coronary artery disease, myocardial infarction, and extrinsic asthma.
58	BRAINOT09	The library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus who died at 23 weeks' gestation.
59	ENDCNOT02	The library was constructed using RNA isolated from dermal microvascular endothelial cells removed from a 30-year-old Caucasian female.
60	HIPONON02	This normalized library was constructed using 1.13 million independent clones from a hippocampus library. RNA was isolated from the hippocampus tissue of a 72-year-old Caucasian female who died from an intracranial bleed. Patient history included nose cancer, hypertension, and arthritis. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9228).
61	OVARNOT02	The library was constructed using RNA isolated from ovarian tissue removed from a 59-year-old Caucasian female who died of a myocardial infarction. Patient history included cardiomyopathy, coronary artery disease, myocardial infarction, hypercholesterolemia, hypotension, and arthritis.
62	OVARNOT02	The library was constructed using RNA isolated from ovarian tissue removed from a 59-year-old Caucasian female who died of a myocardial infarction. Patient history included cardiomyopathy, coronary artery disease, myocardial infarction, hypercholesterolemia, hypotension, and arthritis.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Description
63	ADRETUT01	The library was constructed using RNA isolated from right adrenal tumor tissue removed from a 50-year-old Turkish male during a unilateral adrenalectomy. Pathology indicated a metastatic renal cell carcinoma that formed a circumscribed, spongy, hemorrhagic nodule situated in the region of the medulla. The patient presented with corticoadrenal insufficiency, incisional hernia, and non-alcoholic steato hepatitis. Patient history included renal cell carcinoma. Family history included liver cancer.
64	GBLANOT01	The library was constructed using RNA isolated from diseased gallbladder tissue removed from a 53-year-old Caucasian female during a cholecystectomy. Pathology indicated mild chronic cholecystitis and cholelithiasis with approximately 150 mixed gallstones. Family history included benign hypertension.
65	LUNGTUT09	The library was constructed using RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma and a metastatic tumor. Patient history included type II diabetes, thyroid disorder, depressive disorder, hyperlipidemia, esophageal ulcer, and tobacco use.
66	PONSAZT01	The library was constructed using RNA isolated from diseased pons tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
67	293TF1T01	The library was constructed using RNA isolated from a transformed embryonal cell line (293-EBNA) derived from kidney epithelial tissue. The cells were transformed with adenovirus 5 DNA.
68	ADRENOT14	The library was constructed using RNA isolated from adrenal gland tissue removed from an 8-year-old Black male who died from anoxia.
69	BRAVXT03	The library was constructed using RNA isolated from treated astrocytes removed from the brain of a female fetus who died at 22 weeks' gestation. The cells were treated with tumor necrosis factor (TNF) alpha and interleukin 1 (IL-1), 10ng/ml each for 24 hours.

Table 4 (cont.)

70	293TF2T01	The library was constructed using RNA isolated from a treated, transformed embryonal cell line (293-EBNA) derived from kidney epithelial tissue. The cells were treated with 5-aza-2'-deoxycytidine and transformed with adenovirus 5 DNA.
71	THP1NOB01	Library was constructed using RNA isolated from cultured, unstimulated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia. RNA was isolated from 2x10 ⁸ cells using GuSCN lysis, followed by DNase treatment.
72	TESTNOT01	Library was constructed using RNA isolated from the testicular tissue of a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
73	LUNGNOT09	Library was constructed using RNA isolated from the lung tissue of a 23-week-old Caucasian male fetus. The pregnancy was terminated following a diagnosis by ultrasound of infantile polycystic kidney disease.
74	PROSNOT15	Library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
75	PROSNOT14	Library was constructed using RNA isolated from diseased prostate tissue removed from a 60-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+4). Family history included benign hypertension, cerebrovascular disease, and arteriosclerotic coronary artery disease.
76	SKINBIT01	Library was constructed using RNA isolated from diseased skin tissue of the left lower leg. Patient history included erythema nodosum of the left lower leg.
77	CORPNOT02	Library was constructed using RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
78	BRAITUT02	Library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.

Table 4 (cont.)

79	BRSTNOT07	Library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.
80	KIDNTUT13	Library was constructed using RNA isolated from kidney tumor tissue removed from a 51-year-old Caucasian female during a nephroureterectomy. Pathology indicated a grade 3 renal cell carcinoma. Family history included calculus of the kidney, colon cancer, and type II diabetes.
81	UTRSNOT16	Library was constructed using RNA isolated from uterine endometrial tissue removed from a 48-year-old Caucasian female during a vaginal hysterectomy, rectocele repair, and bilateral salpingo-oophorectomy. Pathology indicated chronic cervicitis, and the endometrium was weakly proliferative. Pathology for the associated tumor tissue indicated a single submucosal leiomyoma. Patient history included hyperlipidemia and meningitis. Family history included benign hypertension, hyperlipidemia, atrial fibrillation, atherosclerotic coronary artery disease, and type II diabetes.
82	UTRMTMT01	Library was constructed using RNA isolated from myometrial tissue removed from a 45-year-old Caucasian female during vaginal hysterectomy and bilateral salpingo-oophorectomy. Pathology indicated the myometrium was negative for tumor. Pathology for the associated tumor tissue indicated multiple (23) subserosal, intramural, and submucosal leiomyomata. Patient history included extrinsic asthma without status asthmaticus and normal delivery. Family history included cerebrovascular disease, depression, and atherosclerotic coronary artery disease.
83	EOSINOT03	This library was constructed using RNA isolated from pooled diseased eosinophils obtained from allergic asthmatic individuals.
84	EOSINOT02	This library was constructed using RNA isolated from pooled eosinophils obtained from allergic asthmatic individuals.
85	CRBLNOT01	This library was constructed using RNA isolated from the cerebellum tissue of a 69-year-old Caucasian male who died from chronic obstructive pulmonary disease. Patient history included myocardial infarction, hypertension, and osteoarthritis.
86	SYNOOAT01	This library was constructed using RNA isolated from the knee synovial membrane tissue of an 82-year-old female with osteoarthritis.
87	BRSTNOT03	This library was constructed using RNA isolated from diseased breast tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy. Pathology for the associated tumor tissue indicated residual invasive grade 3 mammary ductal adenocarcinoma. Patient history included kidney infection and condyloma acuminatum.

			Family history included benign hypertension, hyperlipidemia, and a malignant neoplasm of the colon.
88	LUNGN0T03		This library was constructed using RNA isolated from lung tissue of a 79-year-old Caucasian male. Pathology for the associated tumor tissue indicated grade 4 carcinoma. Patient history included a benign prostate neoplasm and atherosclerosis.
89	COLN0T13		This library was constructed using RNA isolated from ascending colon tissue of a 28-year-old Caucasian male with moderate chronic ulcerative colitis.
90	LARTUT02		This library was constructed using RNA isolated from a myxoma removed from the left atrium of a 43-year-old Caucasian male during annuloplasty. Pathology indicated atrial myxoma. Patient history included pulmonary insufficiency, acute myocardial infarction, atherosclerotic coronary artery disease, hyperlipidemia, and tobacco use. Family history included benign hypertension, acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
91	PROSN0T15		This library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
92	PROSTUT10		This library was constructed using RNA isolated from prostatic tumor tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated an adenocarcinoma (Gleason grade 2+3). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer and secondary bone cancer.
93	PROSTUT12		This library was constructed using RNA isolated from prostate tumor tissue removed from a 65-year-old Caucasian male during a radical prostatectomy. Pathology indicated an adenocarcinoma (Gleason grade 2+2). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA).
94	TESTN0T03		This library was constructed using RNA isolated from testicular tissue removed from a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
95	BRAIN0N01		This library was constructed and normalized from 4.88 million independent clones from a brain library. RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.

Table 4 (cont.)

96	ISLTNOT01	This library was constructed using RNA isolated from a pooled collection of pancreatic islet cells.
97	COLNTUT16	This library was constructed using RNA isolated from colon tumor tissue obtained from a 60-year-old Caucasian male during a left hemicolectomy. Pathology indicated an invasive grade 2 adenocarcinoma, forming a sessile mass. Patient history included thrombophlebitis, inflammatory polyarthropathy, prostatic inflammatory disease, and depressive disorder. Previous surgeries included resection of the rectum. Family history included atherosclerotic coronary artery disease and colon cancer.
98	THYRNOT10	This library was constructed using RNA isolated from the diseased left thyroid tissue removed from a 30-year-old Caucasian female during a unilateral thyroid lobectomy and parathyroid reimplantation. Pathology indicated lymphocytic thyroiditis.
99	PROSBPT03	This library was constructed using RNA isolated from diseased prostate tissue removed from a 59-year-old Caucasian male during a radical prostatectomy and regional lymph node excision. Pathology indicated benign prostatic hyperplasia (BPH). Pathology for the associated tumor indicated adenocarcinoma, Gleason grade 3+3. The patient presented with elevated prostate specific antigen (PSA), benign hypertension, and hyperlipidemia. Family history included cerebrovascular disease, benign hypertension and prostate cancer.
100	BMARNOT03	This library was constructed using RNA isolated from the left tibial bone marrow tissue of a 16-year-old Caucasian male during a partial left tibial osteotomy with free skin graft. Patient history included an abnormality of the red blood cells. Family history included osteoarthritis.
101	UTRSNOT05	This library was constructed using RNA isolated from the uterine tissue of a 45-year-old Caucasian female during a total abdominal hysterectomy and total colectomy. Pathology for the associated tumor tissue indicated multiple leiomyomas of the myometrium and a grade 2 colonic adenocarcinoma of the cecum. Patient history included multiple sclerosis and mitral valve disorder. Family history included type I diabetes, cerebrovascular disease, atherosclerotic coronary artery disease, malignant skin neoplasm, hypertension, and malignant neoplasm of the colon.

Table 4 (cont.)

102	LUNGN0T35	This library was constructed using RNA isolated from lung tissue removed from a 62-year-old Caucasian female. Pathology for the associated tumor tissue indicated a grade 1 spindle cell carcinoma forming a nodule. Patient history included depression, thrombophlebitis, and hyperlipidemia. Family history included cerebrovascular disease, atherosclerotic coronary artery disease, breast cancer, colon cancer, type II diabetes, and malignant skin melanoma.
103	THYMNOT11	This library was constructed using RNA isolated from thymus tissue removed from a 2-year-old Caucasian female during a thymectomy and patch closure of left atrioventricular fistula. The patient presented with congenital heart abnormalities. Patient history included double inlet left ventricle and a rudimentary right ventricle, pulmonary hypertension, cyanosis, subaortic stenosis, seizures, and a fracture of the skull base. Family history included reflux neuropathy.
104	KIDNNOT34	This library was constructed using RNA isolated from left kidney tissue obtained from an 8-year-old Caucasian male who died from an intracranial hemorrhage.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value= 1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value= 1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score \geq GCG-specified "HIGH" value for that particular Prosite motif. Generally, score = 1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score = 120 or greater; Match length = 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score = 3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <i>supra</i> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

5 a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52,

10

15 b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52,

20

25 c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52, and

30

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide encoding a polypeptide of claim 2.

5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID

NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, and SEQ ID NO:104.

- 5 6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
7. A cell transformed with a recombinant polynucleotide of claim 6.
8. A transgenic organism comprising a recombinant polynucleotide of claim 6.
- 10 9. A method for producing a polypeptide of claim 1, the method comprising:
- a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of
- 15 claim 1, and
- b) recovering the polypeptide so expressed.
10. An isolated antibody which specifically binds to a polypeptide of claim 1.
- 20 11. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:
- a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104,
- b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104,
- 25 c) a polynucleotide sequence complementary to a),
- d) a polynucleotide sequence complementary to b), and
- e) an RNA equivalent of a)-d).
12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a
- 30 polynucleotide of claim 11.
13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:
- a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides
- 35 comprising a sequence complementary to said target polynucleotide in the sample, and which probe

specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

5

14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

10 a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

15 16. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

17. A pharmaceutical composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

18. A method for treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition of claim 16.

19. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

35 a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting agonist activity in the sample.

20. A pharmaceutical composition comprising an agonist compound identified by a method of claim 19 and a pharmaceutically acceptable excipient.

5

21. A method for treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 20.

10 22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

15 23. A pharmaceutical composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

24. A method for treating a disease or condition associated with overexpression of functional INTRA, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 23.

25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

26. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

- a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,
- b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and

c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

5

27. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, and
- 10 b) detecting altered expression of the target polynucleotide.

SEQUENCE LISTING

<110> INCYTE GENOMICS, INC.

YUE, Henry
TANG, Y. Tom
HILLMAN, Jennifer L.
LAL, Preeti
BANDMAN, Olga
BAUGHN, Mariah R.
AZIMZAI, Yalda
YANG, Junming
REDDY, Roopa
LU, Dyoung Aina M.

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<150> 60/149,640; 60/164,417

<151> 1999-08-17; 1999-11-09

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Gly Glu Ser Leu Arg	Val Asp Thr Ser Leu	Leu Gly Phe Glu His
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Arg	Trp	Gln	Ala	His	Leu	Glu	Phe	Thr	His	Asn	His	Asp	Val	Gly
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Ile Glu Leu Ser	Leu Ile Thr Leu His	Trp Phe Leu Thr Ala	Phe		
	275		280		285
Ala Ser Val Val	Asp Ile Lys Leu Leu	Leu Arg Ile Trp Asp	Leu		
	290		295		300
Phe Phe Tyr Glu	Gly Ser Arg Val Leu	Phe Gln Leu Thr Leu	Gly		
	305		310		315
Met Leu His Leu	Lys Glu Glu Glu Leu	Ile Gln Ser Glu Asn	Ser		
	320		325		330
Ala Ser Ile Phe	Asn Thr Leu Ser Asp	Ile Pro Ser Gln Met	Glu		
	335		340		345
Asp Ala Glu Leu	Leu Leu Gly Val Ala	Met Arg Leu Ala Gly	Ser		
	350		355		360
Leu Thr Asp Val	Ala Val Glu Thr Gln	Arg Arg Lys His Leu	Ala		
	365		370		375
Tyr Leu Ile Ala	Asp Gln Gly Gln Leu	Leu Gly Ala Gly Thr	Leu		
	380		385		390
Thr Asn Leu Ser	Gln Val Val Arg Arg	Arg Thr Gln Arg Arg	Lys		
	395		400		405
Ser Thr Ile Thr	Ala Leu Leu Phe Gly	Glu Asp Asp Leu Glu	Ala		
	410		415		420
Leu Lys Ala Lys	Asn Ile Lys Gln Thr	Glu Leu Val Ala Asp	Leu		
	425		430		435
Arg Glu Ala Ile	Leu Arg Val Ala Arg	His Phe Gln Cys Thr	Asp		
	440		445		450
Pro Lys Asn Cys	Ser Val Glu Leu Thr	Pro Asp Tyr Ser Met	Glu		
	455		460		465
Ser His Gln Arg	Asp His Glu Asn Tyr	Val Ala Cys Ser Arg	Ser		
	470		475		480
His Arg Arg Arg	Ala Lys Ala Leu Leu	Asp Phe Glu Arg His	Asp		
	485		490		495
Asp Asp Glu Leu	Gly Phe Arg Lys Asn	Asp Ile Ile Thr Ile	Val		
	500		505		510
Ser Gln Lys Asp	Glu His Cys Trp Val	Gly Glu Leu Asn Gly	Leu		
	515		520		525
Arg Gly Trp Phe	Pro Ala Lys Phe Val	Glu Val Leu Asp Glu	Arg		
	530		535		540
Ser Lys Glu Tyr	Ser Ile Ala Gly Asp	Asp Ser Val Thr Glu	Gly		
	545		550		555
Val Thr Asp Leu	Val Arg Gly Thr Leu	Cys Pro Ala Leu Lys	Ala		
	560		565		570
Leu Phe Glu His	Gly Leu Lys Lys Pro	Ser Leu Leu Gly Gly	Ala		
	575		580		585
Cys His Pro Trp	Leu Phe Ile Glu Glu	Ala Ala Gly Arg Glu	Val		
	590		595		600
Glu Arg Asp Phe	Ala Ser Val Tyr Ser	Arg Leu Val Leu Cys	Lys		
	605		610		615
Thr Phe Arg Leu	Asp Glu Asp Gly Lys	Val Leu Thr Pro Glu	Glu		
	620		625		630
Leu Leu Tyr Arg	Ala Val Gln Ser Val	Asn Val Thr His Asp	Ala		
	635		640		645
Val His Ala Gln	Met Asp Val Lys Leu	Arg Ser Leu Ile Cys	Val		
	650		655		660
Gly Leu Asn Glu	Gln Val Leu His Leu	Trp Leu Glu Val Leu	Cys		
	665		670		675
Ser Ser Leu Pro	Thr Val Glu Lys Trp	Tyr Gln Pro Trp Ser	Phe		
	680		685		690
Leu Arg Ser Pro	Gly Trp Val Gln Ile	Lys Cys Glu Leu Arg	Val		
	695		700		705
Leu Cys Cys Phe	Ala Phe Ser Leu Ser	Gln Asp Trp Glu Leu	Pro		
	710		715		720
Ala Lys Arg Glu	Ala Gln Gln Pro Leu	Lys Glu Gly Val Arg	Asp		
	725		730		735

Met Leu Val Lys His His Leu Phe Ser Trp Asp Val Asp Gly
740 745

<210> 7
<211> 139
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2162179CD1

<400> 7
Met Ala Asp Glu Lys Asp Arg Glu Glu Ile Ile Val Ala Glu Phe
1 5 10 15
His Lys Lys Ile Lys Glu Ala Phe Glu Val Phe Asp His Glu Ser
20 25 30
Asn Asn Thr Val Asp Val Arg Glu Ile Gly Thr Ile Ile Arg Ser
35 40 45
Leu Gly Cys Cys Pro Thr Glu Gly Glu Leu His Asp Leu Ile Ala
50 55 60
Glu Val Glu Glu Glu Glu Pro Thr Gly Tyr Ile Arg Phe Glu Lys
65 70 75
Phe Leu Pro Val Met Thr Glu Ile Leu Leu Glu Arg Lys Tyr Arg
80 85 90
Pro Ile Pro Glu Asp Val Leu Leu Arg Ala Phe Glu Val Leu Asp
95 100 105
Ser Ala Lys Arg Gly Phe Leu Thr Lys Asp Glu Leu Ile Lys Tyr
110 115 120
Met Thr Glu Glu Gly Lys Cys Asp Leu Leu Leu Ile Thr Met Thr
125 130 135
Tyr Val Arg Asn

<210> 8
<211> 539
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2244706CD1

<400> 8
Met Val Gly Lys Pro Val His Lys Gly Ser Glu Ser Pro Asn Ser
1 5 10 15
Phe Leu Asp Gln Glu Tyr Arg Lys Arg Phe Asn Ile Val Glu Glu
20 25 30
Asp Thr Val Leu Tyr Cys Tyr Glu Tyr Glu Lys Gly Arg Ser Ser
35 40 45
Ser Gln Gly Arg Arg Glu Ser Thr Pro Thr Tyr Gly Lys Leu Arg
50 55 60
Pro Ile Ser Met Pro Val Glu Tyr Asn Trp Val Gly Asp Tyr Glu
65 70 75
Asp Pro Asn Lys Met Lys Arg Asp Ser Arg Arg Glu Asn Ser Leu
80 85 90
Leu Arg Tyr Met Ser Asn Glu Lys Ile Ala Gln Glu Glu Tyr Met
95 100 105
Phe Gln Arg Asn Ser Lys Lys Asp Thr Gly Lys Lys Ser Lys Lys
110 115 120
Lys Gly Asp Lys Ser Asn Ser Pro Thr His Tyr Ser Leu Leu Pro
125 130 135
Ser Leu Gln Met Asp Ala Leu Arg Gln Asp Ile Met Gly Thr Pro
140 145 150
Val Pro Glu Thr Thr Leu Tyr His Thr Phe Gln Gln Ser Ser Leu
155 160 165
Gln His Lys Ser Lys Lys Lys Asn Lys Gly Pro Ile Ala Gly Lys
170 175 180
Ser Lys Arg Arg Ile Ser Cys Lys Asp Leu Gly Arg Gly Asp Cys

				185					190					195
Glu	Gly	Trp	Leu	Trp	Lys	Lys	Lys	Asp	Ala	Lys	Ser	Tyr	Phe	Ser
				200					205					210
Gln	Lys	Trp	Lys	Lys	Tyr	Trp	Phe	Val	Leu	Lys	Asp	Ala	Ser	Leu
				215					220					225
Tyr	Trp	Tyr	Ile	Asn	Glu	Glu	Asp	Glu	Lys	Ala	Glu	Gly	Phe	Ile
				230					235					240
Ser	Leu	Pro	Glu	Phe	Lys	Ile	Asp	Arg	Ala	Ser	Glu	Cys	Arg	Lys
				245					250					255
Lys	Tyr	Ala	Phe	Lys	Ala	Cys	His	Pro	Lys	Ile	Lys	Ser	Phe	Tyr
				260					265					270
Phe	Ala	Ala	Glu	His	Leu	Asp	Asp	Met	Asn	Arg	Trp	Leu	Asn	Arg
				275					280					285
Ile	Asn	Met	Leu	Thr	Ala	Gly	Tyr	Ala	Glu	Arg	Glu	Arg	Ile	Lys
				290					295					300
Gln	Glu	Gln	Asp	Tyr	Trp	Ser	Glu	Ser	Asp	Lys	Glu	Glu	Ala	Asp
				305					310					315
Thr	Pro	Ser	Thr	Pro	Lys	Gln	Asp	Ser	Pro	Pro	Pro	Pro	Tyr	Asp
				320					325					330
Thr	Tyr	Pro	Arg	Pro	Pro	Ser	Met	Ser	Cys	Ala	Ser	Pro	Tyr	Val
				335					340					345
Glu	Ala	Lys	His	Ser	Arg	Leu	Ser	Ser	Thr	Glu	Thr	Ser	Gln	Ser
				350					355					360
Gln	Ser	Ser	His	Glu	Glu	Phe	Arg	Gln	Glu	Val	Thr	Gly	Ser	Ser
				365					370					375
Ala	Val	Ser	Pro	Ile	Arg	Lys	Thr	Ala	Ser	Gln	Arg	Arg	Ser	Trp
				380					385					390
Gln	Asp	Leu	Ile	Glu	Thr	Pro	Leu	Thr	Ser	Ser	Gly	Leu	His	Tyr
				395					400					405
Leu	Gln	Thr	Leu	Pro	Leu	Glu	Asp	Ser	Val	Phe	Ser	Asp	Ser	Ala
				410					415					420
Ala	Ile	Ser	Pro	Glu	His	Arg	Arg	Gln	Ser	Thr	Leu	Pro	Thr	Gln
				425					430					435
Lys	Cys	His	Leu	Gln	Asp	His	Tyr	Gly	Pro	Tyr	Pro	Leu	Ala	Glu
				440					445					450
Ser	Glu	Met	Met	Gln	Val	Leu	Asn	Gly	Asn	Gly	Gly	Lys	Pro	Arg
				455					460					465
Arg	Phe	Thr	Leu	Pro	Arg	Asp	Ser	Gly	Phe	Asn	His	Cys	Cys	Leu
				470					475					480
Asn	Ala	Pro	Val	Ser	Ala	Cys	Asp	Pro	Gln	Asp	Asp	Val	Gln	Pro
				485					490					495
Pro	Glu	Val	Glu	Glu	Glu	Glu	Asp	Asp	Glu	Glu	Glu	Ala	Trp	Glu
				500					505					510
Ala	Ala	Gly	Gly	Asn	Met	Gly	Glu	Lys	Ser	Leu	Phe	Thr	Ala	Arg
				515					520					525
Val	Gly	Arg	Pro	Phe	Met	Gln	Asn	Gly	Ser	Thr	Leu	Trp	His	
				530					535					

<210> 9

<211> 319

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2316805CD1

<400> 9

Met	Asp	Pro	Gln	Asn	Gln	His	Gly	Ser	Gly	Ser	Ser	Leu	Val	Val
1				5					10					15
Ile	Gln	Gln	Pro	Ser	Leu	Asp	Ser	Arg	Gln	Arg	Leu	Asp	Tyr	Glu
				20					25					30
Arg	Glu	Ile	Gln	Pro	Thr	Ala	Ile	Leu	Ser	Leu	Asp	Gln	Ile	Lys
				35					40					45
Ala	Ile	Arg	Gly	Ser	Asn	Glu	Tyr	Thr	Glu	Gly	Pro	Ser	Val	Val
				50					55					60
Lys	Arg	Pro	Ala	Pro	Arg	Thr	Ala	Pro	Arg	Gln	Glu	Lys	His	Glu
				65					70					75

Arg	Thr	His	Glu	Ile	Ile	Pro	Ile	Asn	Val	Asn	Asn	Asn	Tyr	Glu
				80					85					90
His	Arg	His	Thr	Ser	His	Leu	Gly	His	Ala	Val	Leu	Pro	Ser	Asn
				95					100					105
Ala	Arg	Gly	Pro	Ile	Leu	Ser	Arg	Ser	Thr	Ser	Thr	Gly	Ser	Ala
				110					115					120
Ala	Ser	Ser	Gly	Ser	Asn	Ser	Ser	Ala	Ser	Ser	Glu	Gln	Gly	Leu
				125					130					135
Leu	Gly	Arg	Ser	Pro	Pro	Thr	Arg	Pro	Val	Pro	Gly	His	Arg	Ser
				140					145					150
Glu	Arg	Ala	Ile	Arg	Thr	Gln	Pro	Lys	Gln	Leu	Ile	Val	Asp	Asp
				155					160					165
Leu	Lys	Gly	Ser	Leu	Lys	Glu	Asp	Leu	Thr	Gln	His	Lys	Phe	Ile
				170					175					180
Cys	Glu	Gln	Cys	Gly	Lys	Cys	Lys	Cys	Gly	Glu	Cys	Thr	Ala	Pro
				185					190					195
Arg	Thr	Leu	Pro	Ser	Cys	Leu	Ala	Cys	Asn	Arg	Gln	Cys	Leu	Cys
				200					205					210
Ser	Ala	Glu	Ser	Met	Val	Glu	Tyr	Gly	Thr	Cys	Met	Cys	Leu	Val
				215					220					225
Lys	Gly	Ile	Phe	Tyr	His	Cys	Ser	Asn	Asp	Asp	Glu	Gly	Asp	Ser
				230					235					240
Tyr	Ser	Asp	Asn	Pro	Cys	Ser	Cys	Ser	Gln	Ser	His	Cys	Cys	Ser
				245					250					255
Arg	Tyr	Leu	Cys	Met	Gly	Ala	Met	Ser	Leu	Phe	Leu	Pro	Cys	Leu
				260					265					270
Leu	Cys	Tyr	Pro	Pro	Ala	Lys	Gly	Cys	Leu	Lys	Leu	Cys	Arg	Arg
				275					280					285
Cys	Tyr	Asp	Trp	Ile	His	Arg	Pro	Gly	Cys	Arg	Cys	Lys	Asn	Ser
				290					295					300
Asn	Thr	Val	Tyr	Cys	Lys	Leu	Glu	Ser	Cys	Pro	Ser	Arg	Gly	Gln
				305					310					315

Gly Lys Pro Ser

<210> 10

<211> 747

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2320010CD1

<400> 10

Met	Gly	Lys	Arg	Asn	Ile	Ala	Arg	Val	His	Asp	Ala	Trp	Leu	Ser
1				5					10					15
Lys	His	Phe	Gly	Ile	Asp	Arg	Lys	Ser	Gln	Thr	Met	Pro	Ala	Leu
				20					25					30
Arg	Asn	Arg	Ser	Gly	Val	Met	Gln	Ala	Arg	Leu	Gln	His	Leu	Ser
				35					40					45
Ser	Leu	Glu	Ser	Ser	Phe	Thr	Leu	Asn	His	Ser	Ser	Thr	Thr	Thr
				50					55					60
Glu	Ala	Asp	Ile	Phe	His	Gln	Ala	Leu	Leu	Ala	Ala	Asn	Thr	Ala
				65					70					75
Thr	Glu	Val	Ser	Leu	Thr	Val	Leu	Asp	Thr	Ile	Ser	Phe	Phe	Thr
				80					85					90
Gln	Cys	Phe	Lys	Thr	Gln	Leu	Leu	Asn	Asn	Asp	Gly	His	Asn	Pro
				95					100					105
Leu	Met	Lys	Lys	Val	Phe	Asp	Ile	His	Leu	Ala	Phe	Leu	Lys	Asn
				110					115					120
Gly	Gln	Ser	Glu	Val	Ser	Leu	Lys	His	Val	Phe	Ala	Ser	Leu	Arg
				125					130					135
Ala	Phe	Ile	Ser	Lys	Phe	Pro	Ser	Ala	Phe	Phe	Lys	Gly	Arg	Val
				140					145					150
Asn	Met	Cys	Ala	Ala	Phe	Cys	Tyr	Glu	Val	Leu	Lys	Cys	Cys	Thr
				155					160					165
Ser	Lys	Ile	Ser	Ser	Thr	Arg	Asn	Glu	Ala	Ser	Ala	Leu	Leu	Tyr

Leu	Leu	Met	Arg	Asn	Asn	Phe	Glu	Tyr	Thr	Lys	Arg	Lys	Thr	Phe	170	175	180
				185					190					195			
Leu	Arg	Thr	His	Leu	Gln	Ile	Ile	Ile	Ala	Val	Ser	Gln	Leu	Ile			
				200					205					210			
Ala	Asp	Val	Ala	Leu	Ser	Gly	Gly	Ser	Arg	Phe	Gln	Glu	Ser	Leu			
				215					220					225			
Phe	Ile	Ile	Asn	Asn	Phe	Ala	Asn	Ser	Asp	Arg	Pro	Met	Lys	Ala			
				230					235					240			
Thr	Ala	Phe	Pro	Ala	Glu	Val	Lys	Asp	Leu	Thr	Lys	Arg	Ile	Arg			
				245					250					255			
Thr	Val	Leu	Met	Ala	Thr	Ala	Gln	Met	Lys	Glu	His	Glu	Lys	Asp			
				260					265					270			
Pro	Glu	Met	Leu	Ile	Asp	Leu	Gln	Tyr	Ser	Leu	Ala	Lys	Ser	Tyr			
				275					280					285			
Ala	Ser	Thr	Pro	Glu	Leu	Arg	Lys	Thr	Trp	Leu	Asp	Ser	Met	Ala			
				290					295					300			
Lys	Ile	His	Val	Lys	Asn	Gly	Asp	Phe	Ser	Glu	Ala	Ala	Met	Cys			
				305					310					315			
Tyr	Val	His	Val	Ala	Ala	Leu	Val	Ala	Glu	Phe	Leu	His	Arg	Lys			
				320					325					330			
Lys	Leu	Phe	Pro	Asn	Gly	Cys	Ser	Ala	Phe	Lys	Lys	Ile	Thr	Pro			
				335					340					345			
Asn	Ile	Asp	Glu	Glu	Gly	Ala	Met	Lys	Glu	Asp	Ala	Gly	Met	Met			
				350					355					360			
Asp	Val	His	Tyr	Ser	Glu	Glu	Val	Leu	Leu	Glu	Leu	Leu	Glu	Gln			
				365					370					375			
Cys	Val	Asp	Gly	Leu	Trp	Lys	Ala	Glu	Arg	Tyr	Glu	Ile	Ile	Ser			
				380					385					390			
Glu	Ile	Ser	Lys	Leu	Ile	Val	Pro	Ile	Tyr	Glu	Lys	Arg	Arg	Glu			
				395					400					405			
Phe	Glu	Lys	Leu	Thr	Gln	Val	Tyr	Arg	Thr	Leu	His	Gly	Ala	Tyr			
				410					415					420			
Thr	Lys	Ile	Leu	Glu	Val	Met	His	Thr	Lys	Lys	Arg	Leu	Leu	Gly			
				425					430					435			
Thr	Phe	Phe	Arg	Val	Ala	Phe	Tyr	Gly	Gln	Ser	Phe	Phe	Glu	Glu			
				440					445					450			
Glu	Asp	Gly	Lys	Glu	Tyr	Ile	Tyr	Lys	Glu	Pro	Lys	Leu	Thr	Gly			
				455					460					465			
Leu	Ser	Glu	Ile	Ser	Leu	Arg	Leu	Val	Lys	Leu	Tyr	Gly	Glu	Lys			
				470					475					480			
Phe	Gly	Thr	Glu	Asn	Val	Lys	Ile	Ile	Gln	Asp	Ser	Asp	Lys	Val			
				485					490					495			
Asn	Ala	Lys	Glu	Leu	Asp	Pro	Lys	Tyr	Ala	His	Ile	Gln	Val	Thr			
				500					505					510			
Tyr	Val	Lys	Pro	Tyr	Phe	Asp	Asp	Lys	Glu	Leu	Thr	Glu	Arg	Lys			
				515					520					525			
Thr	Glu	Phe	Glu	Arg	Asn	His	Asn	Ile	Ser	Arg	Phe	Val	Phe	Glu			
				530					535					540			
Ala	Pro	Tyr	Thr	Leu	Ser	Gly	Lys	Lys	Gln	Gly	Cys	Ile	Glu	Glu			
				545					550					555			
Gln	Cys	Lys	Arg	Arg	Thr	Ile	Leu	Thr	Thr	Ser	Asn	Ser	Phe	Pro			
				560					565					570			
Tyr	Val	Lys	Lys	Arg	Ile	Pro	Ile	Asn	Cys	Glu	Gln	Gln	Ile	Asn			
				575					580					585			
Leu	Lys	Pro	Ile	Asp	Val	Ala	Thr	Asp	Glu	Ile	Lys	Asp	Lys	Thr			
				590					595					600			
Ala	Glu	Leu	Gln	Lys	Leu	Cys	Ser	Ser	Thr	Asp	Val	Asp	Met	Ile			
				605					610					615			
Gln	Leu	Gln	Leu	Lys	Leu	Gln	Gly	Cys	Val	Ser	Val	Gln	Val	Asn			
				620					625					630			
Ala	Gly	Pro	Leu	Ala	Tyr	Ala	Arg	Ala	Phe	Leu	Asn	Asp	Ser	Gln			
				635					640					645			
Ala	Ser	Lys	Tyr	Pro	Pro	Lys	Lys	Val	Ser	Glu	Leu	Lys	Asp	Met			
				650					655					660			
Phe	Arg	Lys	Phe	Ile	Gln	Ala	Cys	Ser	Ile	Ala	Leu	Glu	Leu	Asn			
				665					670					675			

Glu	Arg	Leu	Ile	Lys	Glu	Asp	Gln	Val	Glu	Tyr	His	Glu	Gly	Leu
				680					685					690
Lys	Ser	Asn	Phe	Arg	Asp	Met	Val	Lys	Glu	Leu	Ser	Asp	Ile	Ile
				695					700					705
His	Glu	Gln	Ile	Leu	Gln	Glu	Asp	Thr	Met	His	Ser	Pro	Trp	Met
				710					715					720
Ser	Asn	Thr	Leu	His	Val	Phe	Cys	Ala	Ile	Ser	Gly	Thr	Ser	Ser
				725					730					735
Asp	Arg	Gly	Tyr	Gly	Ser	Pro	Arg	Tyr	Ala	Glu	Val			
				740					745					

<210> 11

<211> 266

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2564901CD1

<400> 11

Met	Gln	Gly	Ser	Thr	Arg	Arg	Met	Gly	Val	Met	Thr	Asp	Val	His
1				5					10					15
Arg	Arg	Phe	Leu	Gln	Leu	Leu	Met	Thr	His	Gly	Val	Leu	Glu	Glu
				20					25					30
Trp	Asp	Val	Lys	Arg	Leu	Gln	Thr	His	Cys	Tyr	Lys	Val	His	Asp
				35					40					45
Arg	Asn	Ala	Thr	Val	Asp	Lys	Leu	Glu	Asp	Phe	Ile	Asn	Asn	Ile
				50					55					60
Asn	Ser	Val	Leu	Glu	Ser	Leu	Tyr	Ile	Glu	Ile	Lys	Arg	Gly	Val
				65					70					75
Thr	Glu	Asp	Asp	Gly	Arg	Pro	Ile	Tyr	Ala	Leu	Val	Asn	Leu	Ala
				80					85					90
Thr	Thr	Ser	Ile	Ser	Lys	Met	Ala	Thr	Asp	Phe	Ala	Glu	Asn	Glu
				95					100					105
Leu	Asp	Leu	Phe	Arg	Lys	Ala	Leu	Glu	Leu	Ile	Ile	Asp	Ser	Glu
				110					115					120
Thr	Gly	Phe	Ala	Ser	Ser	Thr	Asn	Ile	Leu	Asn	Leu	Val	Asp	Gln
				125					130					135
Leu	Lys	Gly	Lys	Lys	Met	Arg	Lys	Lys	Glu	Ala	Glu	Gln	Val	Leu
				140					145					150
Gln	Lys	Phe	Val	Gln	Asn	Lys	Trp	Leu	Ile	Glu	Lys	Glu	Gly	Glu
				155					160					165
Phe	Thr	Leu	His	Gly	Arg	Ala	Ile	Leu	Glu	Met	Glu	Gln	Tyr	Ile
				170					175					180
Arg	Glu	Thr	Tyr	Pro	Asp	Ala	Val	Lys	Ile	Cys	Asn	Ile	Cys	His
				185					190					195
Ser	Leu	Leu	Ile	Gln	Gly	Gln	Ser	Cys	Glu	Thr	Cys	Gly	Ile	Arg
				200					205					210
Met	His	Leu	Pro	Cys	Val	Ala	Lys	Tyr	Phe	Gln	Ser	Asn	Ala	Glu
				215					220					225
Pro	Arg	Cys	Pro	His	Cys	Asn	Asp	Tyr	Trp	Pro	His	Glu	Ile	Pro
				230					235					240
Lys	Val	Phe	Asp	Pro	Glu	Lys	Glu	Arg	Glu	Ser	Gly	Val	Leu	Lys
				245					250					255
Ser	Asn	Lys	Lys	Ser	Leu	Arg	Ser	Arg	Gln	His				
				260					265					

<210> 12

<211> 345

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2615168CD1

<400> 12

Met Ser Val Thr Gly Gly Lys Met Ala Pro Ser Leu Thr Gln Glu

1	5	10	15
Ile Leu Ser His	Leu Gly Leu Ala Ser	Lys Thr Ala Ala Trp	Gly
	20	25	30
Thr Leu Gly Thr	Leu Arg Thr Phe Leu	Asn Phe Ser Val Asp	Lys
	35	40	45
Asp Ala Gln Arg	Leu Leu Arg Ala Ile	Thr Gly Gln Gly Val	Asp
	50	55	60
Arg Ser Ala Ile	Val Asp Val Leu Thr	Asn Arg Ser Arg Glu	Gln
	65	70	75
Arg Gln Leu Ile	Ser Arg Asn Phe Gln	Glu Arg Thr Gln Gln	Asp
	80	85	90
Leu Met Lys Ser	Leu Gln Ala Ala Leu	Ser Gly Asn Leu Glu	Arg
	95	100	105
Ile Val Met Ala	Leu Leu Gln Pro Thr	Ala Gln Phe Asp Ala	Gln
	110	115	120
Glu Leu Arg Thr	Ala Leu Lys Ala Ser	Asp Ser Ala Val Asp	Val
	125	130	135
Ala Ile Glu Ile	Leu Ala Thr Arg Thr	Pro Pro Gln Leu Gln	Glu
	140	145	150
Cys Leu Ala Val	Tyr Lys His Asn Phe	Gln Val Glu Ala Val	Asp
	155	160	165
Asp Ile Thr Ser	Glu Thr Ser Gly Ile	Leu Gln Asp Leu Leu	Leu
	170	175	180
Ala Leu Ala Lys	Gly Gly Arg Asp Ser	Tyr Ser Gly Ile Ile	Asp
	185	190	195
Tyr Asn Leu Ala	Glu Gln Asp Val Gln	Ala Leu Gln Arg Ala	Glu
	200	205	210
Gly Pro Ser Arg	Glu Glu Thr Trp Val	Pro Val Phe Thr Gln	Arg
	215	220	225
Asn Pro Glu His	Leu Ile Arg Val Phe	Asp Gln Tyr Gln Arg	Ser
	230	235	240
Thr Gly Gln Glu	Leu Glu Glu Ala Val	Gln Asn Arg Phe His	Gly
	245	250	255
Asp Ala Gln Val	Ala Leu Leu Gly Leu	Ala Ser Val Ile Lys	Asn
	260	265	270
Thr Pro Leu Tyr	Phe Ala Asp Lys Leu	His Gln Ala Leu Gln	Glu
	275	280	285
Thr Glu Pro Asn	Tyr Gln Val Leu Ile	Arg Ile Leu Ile Ser	Arg
	290	295	300
Cys Glu Thr Asp	Leu Leu Ser Ile Arg	Ala Glu Phe Arg Lys	Lys
	305	310	315
Phe Gly Lys Ser	Leu Tyr Ser Ser Leu	Gln Asp Ala Val Lys	Gly
	320	325	330
Asp Cys Gln Ser	Ala Leu Leu Ala Leu	Cys Arg Ala Glu Asp	Met
	335	340	345

<210> 13

<211> 437

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2658329CD1

<400> 13

Met Glu Lys Glu	Leu Arg Ser Thr Ile	Leu Phe Asn Ala Tyr	Lys
1	5	10	15
Lys Glu Ile Phe	Thr Thr Asn Asn Gly	Tyr Lys Ser Met Gln	Lys
	20	25	30
Lys Leu Arg Ser	Asn Trp Lys Ile Gln	Ser Leu Lys Asp Glu	Ile
	35	40	45
Thr Ser Glu Lys	Leu Asn Gly Val Lys	Leu Trp Ile Thr Ala	Gly
	50	55	60
Pro Arg Glu Lys	Phe Thr Ala Ala Glu	Phe Glu Ile Leu Lys	Lys
	65	70	75
Tyr Leu Asp Thr	Gly Gly Asp Val Phe	Val Met Leu Gly Glu	Gly

Gly	Glu	Ser	Arg	Phe	Asp	Thr	Asn	Ile	Asn	Phe	Leu	Leu	Glu	Glu
80									85					90
Tyr	Gly	Ile	Met	Val	Asn	Asn	Asp	Ala	Val	Val	Arg	Asn	Val	Tyr
95									100					105
His	Lys	Tyr	Phe	His	Pro	Lys	Glu	Ala	Leu	Val	Ser	Ser	Gly	Val
110									115					120
Leu	Asn	Arg	Glu	Ile	Ser	Arg	Ala	Ala	Gly	Lys	Ala	Val	Pro	Gly
125									130					135
Ile	Ile	Asp	Glu	Glu	Ser	Ser	Gly	Asn	Asn	Ala	Gln	Ala	Leu	Thr
140									145					150
Phe	Val	Tyr	Pro	Phe	Gly	Ala	Thr	Leu	Ser	Val	Met	Lys	Pro	Ala
155									160					165
Val	Ala	Val	Leu	Ser	Thr	Gly	Ser	Val	Cys	Phe	Pro	Leu	Asn	Arg
170									175					180
Pro	Ile	Leu	Ala	Phe	Tyr	His	Ser	Lys	Asn	Gln	Gly	Gly	Lys	Leu
185									190					195
Ala	Val	Leu	Gly	Ser	Cys	His	Met	Phe	Ser	Asp	Gln	Tyr	Leu	Asp
200									205					210
Lys	Glu	Glu	Asn	Ser	Lys	Ile	Met	Asp	Val	Val	Phe	Gln	Trp	Leu
215									220					225
Thr	Thr	Gly	Asp	Ile	His	Leu	Asn	Gln	Ile	Asp	Ala	Glu	Asp	Pro
230									235					240
Glu	Ile	Ser	Asp	Tyr	Met	Met	Leu	Pro	Tyr	Thr	Ala	Thr	Leu	Ser
245									250					255
Lys	Arg	Asn	Arg	Glu	Cys	Leu	Gln	Glu	Ser	Asp	Glu	Ile	Pro	Arg
260									265					270
Asp	Phe	Thr	Thr	Leu	Phe	Asp	Leu	Ser	Ile	Phe	Gln	Leu	Asp	Thr
275									280					285
Thr	Ser	Phe	His	Ser	Val	Ile	Glu	Ala	His	Glu	Gln	Leu	Asn	Val
290									295					300
Lys	His	Glu	Pro	Leu	Gln	Leu	Ile	Gln	Pro	Gln	Phe	Glu	Thr	Pro
305									310					315
Leu	Pro	Thr	Leu	Gln	Pro	Ala	Val	Phe	Pro	Pro	Ser	Phe	Arg	Glu
320									325					330
Leu	Pro	Pro	Pro	Pro	Leu	Glu	Leu	Phe	Asp	Leu	Asp	Glu	Thr	Phe
335									340					345
Ser	Ser	Glu	Lys	Ala	Arg	Leu	Ala	Gln	Ile	Thr	Asn	Lys	Cys	Thr
350									355					360
Glu	Glu	Asp	Leu	Glu	Phe	Tyr	Val	Arg	Lys	Cys	Gly	Asp	Ile	Leu
365									370					375
Gly	Val	Thr	Ser	Lys	Leu	Pro	Lys	Asp	Gln	Gln	Asp	Ala	Lys	His
380									385					390
Ile	Leu	Glu	His	Val	Phe	Phe	Gln	Val	Val	Glu	Phe	Lys	Lys	Leu
395									400					405
Asn	Gln	Glu	His	Asp	Ile	Asp	Thr	Ser	Glu	Thr	Ala	Phe	Gln	Asn
410									415					420
Asn	Phe								425					430
														435

<210> 14

<211> 441

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2708944CD1

<400> 14

Met	Val	His	Ile	Lys	Lys	Gly	Glu	Leu	Thr	Gln	Glu	Glu	Lys	Glu
1				5					10					15
Leu	Leu	Glu	Val	Ile	Gly	Lys	Gly	Thr	Val	Gln	Glu	Ala	Gly	Thr
				20					25					30
Leu	Leu	Ser	Ser	Lys	Asn	Val	Arg	Val	Asn	Cys	Leu	Asp	Glu	Asn
				35					40					45
Gly	Met	Thr	Pro	Leu	Met	His	Ala	Ala	Tyr	Lys	Gly	Lys	Leu	Asp
				50					55					60

Met Cys Lys Leu Leu Leu Arg His Gly Ala Asp Val Asn Cys His
 65 70 75
 Gln His Glu His Gly Tyr Thr Ala Leu Met Phe Ala Ala Leu Ser
 80 85 90
 Gly Asn Lys Asp Ile Thr Trp Val Met Leu Glu Ala Gly Ala Glu
 95 100 105
 Thr Asp Val Val Asn Ser Val Gly Arg Thr Ala Ala Gln Met Ala
 110 115 120
 Ala Phe Val Gly Gln His Asp Cys Val Thr Ile Ile Asn Asn Phe
 125 130 135
 Phe Pro Arg Glu Arg Leu Asp Tyr Tyr Thr Lys Pro Gln Gly Leu
 140 145 150
 Asp Lys Glu Pro Lys Leu Pro Pro Lys Leu Ala Gly Pro Leu His
 155 160 165
 Lys Ile Ile Thr Thr Thr Asn Leu His Pro Val Lys Ile Val Met
 170 175 180
 Leu Val Asn Glu Asn Pro Leu Leu Thr Glu Glu Ala Ala Leu Asn
 185 190 195
 Lys Cys Tyr Arg Val Met Asp Leu Ile Cys Glu Lys Cys Met Lys
 200 205 210
 Gln Arg Asp Met Asn Glu Val Leu Ala Met Lys Met His Tyr Ile
 215 220 225
 Ser Cys Ile Phe Gln Lys Cys Ile Asn Phe Leu Lys Asp Gly Glu
 230 235 240
 Asn Lys Leu Asp Thr Leu Ile Lys Ser Leu Leu Lys Gly Arg Ala
 245 250 255
 Ser Asp Gly Phe Pro Val Tyr Gln Glu Lys Ile Ile Arg Glu Ser
 260 265 270
 Ile Arg Lys Phe Pro Tyr Cys Glu Ala Thr Leu Leu Gln Gln Leu
 275 280 285
 Val Arg Ser Ile Ala Pro Val Glu Ile Gly Ser Asp Pro Thr Ala
 290 295 300
 Phe Ser Val Leu Thr Gln Ala Ile Thr Gly Gln Val Gly Phe Val
 305 310 315
 Asp Val Glu Phe Cys Thr Thr Cys Gly Glu Lys Gly Ala Ser Lys
 320 325 330
 Arg Cys Ser Val Cys Lys Met Val Ile Tyr Cys Asp Gln Thr Cys
 335 340 345
 Gln Lys Thr His Trp Phe Thr His Lys Lys Ile Cys Lys Asn Leu
 350 355 360
 Lys Asp Ile Tyr Glu Lys Gln Gln Leu Glu Ala Ala Lys Glu Lys
 365 370 375
 Arg Gln Glu Glu Asn His Gly Lys Leu Asp Val Asn Ser Asn Cys
 380 385 390
 Val Asn Glu Glu Gln Pro Glu Ala Glu Val Gly Ile Ser Gln Lys
 395 400 405
 Asp Ser Asn Pro Glu Asp Ser Gly Glu Gly Lys Lys Glu Ser Leu
 410 415 420
 Glu Ser Glu Ala Glu Leu Glu Gly Leu Gln Asp Ala Pro Ala Gly
 425 430 435
 Pro Gln Val Ser Glu Glu 440

<210> 15

<211> 487

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 331501-001

<400> 15

Met Leu Arg Ala Pro Gly Cys Leu Leu Arg Thr Ser Val Ala Pro
 1 5 10 15
 Ala Ala Ala Leu Ala Ala Ala Leu Leu Ser Ser Leu Ala Arg Cys
 20 25 30
 Ser Leu Leu Glu Pro Arg Asp Pro Val Ala Ser Ser Leu Ser Pro

Tyr	Phe	Gly	Thr	Lys	Thr	Arg	Tyr	Glu	Asp	Val	Asn	Pro	Val	Leu	45
Leu	Ser	Gly	Pro	Glu	Ala	Pro	Trp	Arg	Asp	Pro	Glu	Leu	Leu	Glu	60
Gly	Thr	Cys	Thr	Pro	Val	Gln	Leu	Val	Ala	Leu	Ile	Arg	His	Gly	75
Thr	Arg	Tyr	Pro	Thr	Val	Lys	Gln	Ile	Arg	Lys	Leu	Arg	Gln	Leu	90
His	Gly	Leu	Leu	Gln	Ala	Arg	Gly	Ser	Arg	Asp	Gly	Gly	Ala	Ser	105
Ser	Thr	Gly	Ser	Arg	Asp	Leu	Gly	Ala	Ala	Leu	Ala	Asp	Trp	Pro	120
Leu	Trp	Tyr	Ala	Asp	Trp	Met	Asp	Gly	Gln	Leu	Val	Glu	Lys	Gly	135
Arg	Gln	Asp	Met	Arg	Gln	Leu	Ala	Leu	Arg	Leu	Ala	Ser	Leu	Phe	150
Pro	Val	Leu	Phe	Ser	Arg	Glu	Asn	Tyr	Gly	Arg	Leu	Arg	Leu	Ile	165
Thr	Ser	Ser	Lys	His	Arg	Cys	Met	Asp	Ser	Ser	Ala	Ala	Phe	Leu	180
Gln	Gly	Leu	Trp	Gln	His	Tyr	His	Pro	Gly	Leu	Pro	Pro	Pro	Asp	195
Val	Ala	Asp	Met	Glu	Phe	Gly	Pro	Pro	Thr	Val	Asn	Asp	Lys	Leu	210
Met	Arg	Phe	Phe	Asp	His	Cys	Glu	Lys	Phe	Leu	Thr	Glu	Val	Glu	225
Lys	Asn	Ala	Thr	Ala	Leu	Tyr	His	Val	Glu	Ala	Phe	Lys	Thr	Gly	240
Pro	Glu	Met	Gln	Asn	Ile	Leu	Lys	Lys	Val	Ala	Ala	Thr	Leu	Gln	255
Val	Pro	Val	Asn	Asp	Leu	Asn	Ala	Asp	Leu	Ile	Gln	Val	Ala	Phe	270
Phe	Thr	Cys	Ser	Phe	Asp	Leu	Ala	Ile	Lys	Gly	Val	Lys	Ser	Pro	285
Trp	Cys	Asp	Val	Phe	Asp	Ile	Asp	Asp	Ala	Lys	Val	Leu	Glu	Tyr	300
Leu	Asn	Asp	Leu	Lys	Gln	Tyr	Trp	Lys	Arg	Gly	Tyr	Gly	Tyr	Thr	315
Ile	Asn	Ser	Arg	Ser	Ser	Cys	Thr	Leu	Phe	Gln	Asp	Ile	Phe	Gln	330
His	Leu	Asp	Lys	Ala	Val	Glu	Gln	Lys	Gln	Arg	Ser	Gln	Pro	Ile	345
Ser	Ser	Pro	Val	Ile	Leu	Gln	Phe	Gly	His	Ala	Glu	Thr	Leu	Leu	360
Pro	Leu	Leu	Ser	Leu	Met	Gly	Tyr	Phe	Lys	Asp	Lys	Glu	Pro	Leu	375
Thr	Ala	Tyr	Asn	Tyr	Lys	Lys	Gln	Met	His	Arg	Lys	Phe	Arg	Ser	390
Gly	Leu	Ile	Val	Pro	Tyr	Ala	Ser	Asn	Leu	Ile	Phe	Val	Leu	Tyr	405
His	Cys	Glu	Asn	Ala	Lys	Thr	Pro	Lys	Glu	Gln	Phe	Arg	Val	Gln	420
Met	Leu	Leu	Asn	Glu	Lys	Val	Leu	Pro	Leu	Ala	Tyr	Ser	Gln	Glu	435
Thr	Val	Ser	Phe	Tyr	Glu	Asp	Leu	Lys	Asn	His	Tyr	Lys	Asp	Ile	450
Leu	Gln	Ser	Cys	Gln	Thr	Ser	Glu	Glu	Cys	Glu	Leu	Ala	Arg	Ala	465
Asn	Ser	Thr	Ser	Asp	Glu	Leu			475						480

<210> 16
 <211> 282
 <212> PRT
 <213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4155412CD1

<400> 16

Met Val Leu Gly Lys Val Lys Ser Leu Thr Ile Ser Phe Asp Cys 15
 1 5 10
 Leu Asn Asp Ser Asn Val Pro Val Tyr Ser Ser Gly Asp Thr Val 30
 20 25 30
 Ser Gly Arg Val Asn Leu Glu Val Thr Gly Glu Ile Arg Val Lys 45
 35 40 45
 Ser Leu Lys Ile His Ala Arg Gly His Ala Lys Val Arg Trp Thr 60
 50 55 60
 Glu Ser Arg Asn Ala Gly Ser Asn Thr Ala Tyr Thr Gln Asn Tyr 75
 65 70 75
 Thr Glu Glu Val Glu Tyr Phe Asn His Lys Asp Ile Leu Ile Gly 90
 80 85 90
 His Glu Arg Asp Asp Asn Ser Glu Glu Gly Phe His Thr Ile 105
 95 100 105
 His Ser Gly Arg His Glu Tyr Ala Phe Ser Phe Glu Leu Pro Gln 120
 110 115 120
 Thr Pro Leu Ala Thr Ser Phe Glu Gly Arg His Gly Ser Val Arg 135
 125 130 135
 Tyr Trp Val Lys Ala Glu Leu His Arg Pro Trp Leu Leu Pro Val 150
 140 145 150
 Lys Leu Lys Lys Glu Phe Thr Val Phe Glu His Ile Asp Ile Asn 165
 155 160 165
 Thr Pro Ser Leu Leu Ser Pro Gln Ala Gly Thr Lys Glu Lys Thr 180
 170 175 180
 Leu Cys Cys Trp Phe Cys Thr Ser Gly Pro Ile Ser Leu Ser Ala 195
 185 190 195
 Lys Ile Glu Arg Lys Gly Tyr Thr Pro Gly Glu Ser Ile Gln Ile 210
 200 205 210
 Phe Ala Glu Ile Glu Asn Cys Ser Ser Arg Met Val Val Pro Arg 225
 215 220 225
 Gln Pro Phe Thr Lys His Arg Pro Ser Ile Ala Lys Gly Lys Leu 240
 230 235 240
 Arg Glu Leu Asn Ser Leu Trp Leu Thr Cys Val Gly Asn Ser Leu 255
 245 250 255
 Thr Ser Gly Lys Asn Arg Asp Val Glu Met Ala Ser Leu Leu Lys 270
 260 265 270
 Ile Ser Asn Ser Phe Pro Pro Ser Asn Ala Ser Asn 280
 275 280

<210> 17

<211> 581

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4831840CD1

<400> 17

Met Ala Val Ala Gly Ala Val Ser Gly Glu Pro Leu Val His Trp 15
 1 5 10
 Cys Thr Gln Gln Leu Arg Lys Thr Phe Gly Leu Asp Val Ser Glu 30
 20 25 30
 Glu Ile Ile Gln Tyr Val Leu Ser Ile Glu Ser Ala Glu Glu Ile 45
 35 40 45
 Arg Glu Tyr Val Thr Asp Leu Leu Gln Gly Asn Glu Gly Lys Lys 60
 50 55 60
 Gly Gln Phe Ile Glu Glu Leu Ile Thr Lys Trp Gln Lys Asn Asp 75
 65 70 75
 Gln Glu Leu Ile Ser Asp Pro Leu Gln Gln Cys Phe Lys Lys Asp 90
 80 85 90
 Glu Ile Leu Asp Gly Gln Lys Ser Gly Asp His Leu Lys Arg Gly 105
 95 100 105
 Arg Lys Lys Gly Arg Asn Arg Gln Glu Val Pro Ala Phe Thr Glu 110

Pro Asp Thr Thr	110	Ala Glu Val Lys Thr	115	Pro Phe Asp Leu Ala	120
	125		130	Lys Lys Thr Lys Phe	135
Ala Gln Glu Asn	140	Ser Asn Ser Val Lys	145	Lys Lys Thr Lys Phe	150
Asn Leu Tyr Thr	155	Arg Glu Gly Gln Asp	160	Arg Leu Ala Val Leu	165
Pro Gly Arg His	170	Pro Cys Asp Cys Leu	175	Gly Gln Lys His Lys	180
Ile Asn Asn Cys	185	Leu Ile Cys Gly Arg	190	Ile Val Cys Glu Gln	195
Gly Ser Gly Pro	200	Cys Leu Phe Cys Gly	205	Thr Leu Val Cys Thr	210
Glu Glu Gln Asp	215	Ile Leu Gln Arg Asp	220	Ser Asn Lys Ser Gln	225
Leu Leu Lys Lys	230	Leu Met Ser Gly Val	235	Glu Asn Ser Gly Lys	240
Asp Ile Ser Thr	245	Lys Asp Leu Leu Pro	250	His Gln Glu Leu Arg	255
Lys Ser Gly Leu	260	Glu Lys Ala Ile Lys	265	His Lys Asp Lys Leu	270
Glu Phe Asp Arg	275	Thr Ser Ile Arg Arg	280	Thr Gln Val Ile Asp	285
Glu Ser Asp Tyr	290	Phe Ala Ser Asp Ser	295	Asn Gln Trp Leu Ser	300
Leu Glu Arg Glu	305	Thr Leu Gln Lys Arg	310	Glu Glu Glu Leu Arg	315
Leu Arg His Ala	320	Ser Arg Leu Ser Lys	325	Lys Val Thr Ile Asp	330
Ala Gly Arg Lys	335	Ile Leu Glu Glu Glu	340	Asn Ser Leu Ala Glu	345
His Ser Arg Leu	350	Asp Glu Thr Ile Gln	355	Ala Ile Ala Asn Gly	360
Leu Asn Gln Pro	365	Leu Thr Lys Leu Asp	370	Arg Ser Ser Glu Glu	375
Leu Gly Val Leu	380	Val Asn Pro Asn Met	385	Tyr Gln Ser Pro Pro	390
Trp Val Asp His	395	Thr Gly Ala Ala Ser	400	Gln Lys Lys Ala Phe	405
Ser Ser Gly Phe	410	Gly Leu Glu Phe Asn	415	Ser Phe Gln His Gln	420
Arg Ile Gln Asp	425	Gln Glu Phe Gln Glu	430	Gly Phe Asp Gly Gly	435
Cys Leu Ser Val	440	His Gln Pro Trp Ala	445	Ser Leu Leu Val Arg	450
Ile Lys Arg Val	455	Glu Gly Arg Ser Trp	460	Tyr Thr Pro His Arg	465
Arg Leu Trp Ile	470	Ala Ala Thr Ala Lys	475	Lys Pro Ser Pro Gln	480
Val Ser Glu Leu	485	Gln Ala Thr Tyr Arg	490	Leu Leu Arg Gly Lys	495
Val Glu Phe Pro	500	Asn Asp Tyr Pro Ser	505	Gly Cys Leu Leu Gly	510
Val Asp Leu Ile	515	Asp Cys Leu Ser Gln	520	Lys Gln Phe Lys Glu	525
Phe Pro Asp Ile	530	Ser Gln Glu Ser Asp	535	Ser Pro Phe Val Phe	540
Cys Lys Asn Pro	545	Gln Glu Met Val Val	550	Lys Phe Pro Ile Lys	555
Asn Pro Lys Ile	560	Trp Lys Leu Asp Ser	565	Lys Ile His Gln Gly	570
Lys Lys Gly Leu	575	Met Lys Gln Asn Lys	580	Ala Val	

<210> 18

<211> 530

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5676581CD1

<400> 18

Met	Thr	Thr	Arg	Pro	Thr	Ala	Val	Lys	Ala	Thr	Gly	Gly	Leu	Cys	1	5	10	15
Leu	Leu	Gly	Ala	Tyr	Ala	Asp	Ser	Asp	Asp	Asp	Asp	Asn	Asp	Val	20	25	30	35
Ser	Glu	Lys	Leu	Ala	Gln	Ser	Lys	Glu	Thr	Asn	Gly	Asn	Gln	Ser	40	45	50	55
Thr	Asp	Ile	Asp	Ser	Thr	Leu	Ala	Asn	Phe	Leu	Ala	Glu	Ile	Asp	60	65	70	75
Ala	Ile	Thr	Ala	Pro	Gln	Pro	Ala	Ala	Pro	Val	Gly	Ala	Ser	Ala	80	85	90	95
Pro	Pro	Pro	Thr	Pro	Pro	Arg	Pro	Glu	Pro	Lys	Glu	Ala	Ala	Thr	100	105	110	115
Ser	Thr	Leu	Ser	Ser	Ser	Thr	Ser	Asn	Gly	Thr	Asp	Ser	Thr	Gln	120	125	130	135
Thr	Ser	Gly	Trp	Gln	Tyr	Asp	Thr	Gln	Cys	Ser	Leu	Ala	Gly	Val	140	145	150	155
Gly	Ile	Glu	Met	Gly	Asp	Trp	Gln	Glu	Val	Trp	Asp	Glu	Asn	Thr	160	165	170	175
Gly	Cys	Tyr	Tyr	Tyr	Trp	Asn	Thr	Gln	Thr	Asn	Glu	Val	Thr	Trp	180	185	190	195
Glu	Leu	Pro	Gln	Tyr	Leu	Ala	Thr	Gln	Val	Gln	Gly	Leu	Gln	His	200	205	210	215
Tyr	Gln	Pro	Ser	Ser	Val	Pro	Gly	Ala	Glu	Thr	Ser	Phe	Val	Val	220	225	230	235
Asn	Thr	Asp	Ile	Tyr	Ser	Lys	Glu	Lys	Thr	Ile	Ser	Val	Ser	Ser	240	245	250	255
Ser	Lys	Ser	Gly	Pro	Val	Ile	Ala	Lys	Arg	Glu	Val	Lys	Lys	Glu	260	265	270	275
Val	Asn	Glu	Gly	Ile	Gln	Ala	Leu	Ser	Asn	Ser	Glu	Glu	Glu	Lys	280	285	290	295
Lys	Gly	Val	Ala	Ala	Ser	Leu	Leu	Ala	Pro	Leu	Leu	Pro	Glu	Gly	300	305	310	315
Ile	Lys	Glu	Glu	Glu	Glu	Arg	Trp	Arg	Arg	Lys	Val	Ile	Cys	Lys	320	325	330	335
Glu	Glu	Pro	Val	Ser	Glu	Val	Lys	Glu	Thr	Ser	Thr	Thr	Val	Glu	340	345	350	355
Glu	Ala	Thr	Thr	Ile	Val	Lys	Pro	Gln	Glu	Ile	Met	Leu	Asp	Asn	360	365	370	375
Ile	Glu	Asp	Pro	Ser	Gln	Glu	Asp	Leu	Cys	Ser	Val	Val	Gln	Ser	380	385	390	395
Gly	Glu	Ser	Glu	Glu	Glu	Glu	Gln	Asp	Thr	Leu	Glu	Leu	Glu	Glu	400	405	410	415
Leu	Val	Leu	Glu	Arg	Lys	Lys	Ala	Glu	Leu	Arg	Ala	Leu	Glu	Glu	420	425	430	435
Gly	Asp	Gly	Ser	Val	Ser	Gly	Ser	Ser	Pro	Arg	Ser	Asp	Ile	Ser	440	445	450	455
Gln	Pro	Ala	Ser	Gln	Asp	Gly	Met	Arg	Arg	Leu	Met	Ser	Lys	Arg	460	465		
Gly	Lys	Trp	Lys	Met	Phe	Val	Arg	Ala	Thr	Ser	Pro	Glu	Ser	Thr				
Ser	Arg	Ser	Ser	Ser	Lys	Thr	Gly	Arg	Asp	Thr	Pro	Glu	Asn	Gly				
Glu	Thr	Ala	Ile	Gly	Ala	Glu	Asn	Ser	Glu	Lys	Ile	Asp	Glu	Asn				
Ser	Asp	Lys	Glu	Met	Glu	Val	Glu	Glu	Ser	Pro	Glu	Lys	Ile	Lys				
Val	Gln	Thr	Thr	Pro	Lys	Val	Glu	Glu	Glu	Gln	Asp	Leu	Lys	Phe				
Gln	Ile	Gly	Glu	Leu	Ala	Asn	Thr	Leu	Thr	Ser	Lys	Phe	Glu	Phe				
Leu	Gly	Ile	Asn	Arg	Gln	Ser	Ile	Ser	Asn	Phe	His	Val	Leu	Leu				

Leu	Gln	Thr	Glu	Thr	Arg	Ile	Ala	Asp	Trp	Arg	Glu	Gly	Ala	Leu
				470					475					480
Asn	Gly	Asn	Tyr	Leu	Lys	Arg	Lys	Leu	Gln	Asp	Ala	Ala	Glu	Gln
				485					490					495
Leu	Lys	Gln	Tyr	Glu	Ile	Asn	Ala	Thr	Pro	Lys	Gly	Trp	Ser	Cys
				500					505					510
His	Trp	Asp	Arg	Tyr	Ala	Leu	Phe	Ser	Pro	Phe	His	Leu	Ser	Pro
				515					520					525
Leu	Thr	Ser	Gln	Thr										
				530										

<210> 19

<211> 475

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 034159CD1

<400> 19

Met	Gln	Lys	Ser	Thr	Asn	Ser	Asp	Thr	Ser	Val	Glu	Thr	Leu	Asn
1				5					10					15
Ser	Thr	Arg	Gln	Gly	Thr	Gly	Ala	Val	Gln	Met	Arg	Ile	Lys	Asn
				20					25					30
Ala	Asn	Ser	His	His	Asp	Arg	Leu	Ser	Gln	Ser	Lys	Ser	Met	Ile
				35					40					45
Leu	Thr	Asp	Val	Gly	Lys	Val	Thr	Glu	Pro	Ile	Ser	Arg	His	Arg
				50					55					60
Arg	Asn	His	Ser	Gln	His	Ile	Leu	Lys	Asp	Val	Ile	Pro	Pro	Leu
				65					70					75
Glu	Gln	Leu	Met	Val	Glu	Lys	Glu	Gly	Tyr	Leu	Gln	Lys	Ala	Lys
				80					85					90
Ile	Ala	Asp	Gly	Gly	Lys	Lys	Leu	Arg	Lys	Asn	Trp	Ser	Thr	Ser
				95					100					105
Trp	Ile	Val	Leu	Ser	Ser	Arg	Arg	Ile	Glu	Phe	Tyr	Lys	Glu	Ser
				110					115					120
Lys	Gln	Gln	Ala	Leu	Ser	Asn	Met	Lys	Thr	Gly	His	Lys	Pro	Glu
				125					130					135
Ser	Val	Asp	Leu	Cys	Gly	Ala	His	Ile	Glu	Trp	Ala	Lys	Glu	Lys
				140					145					150
Ser	Ser	Arg	Lys	Asn	Val	Phe	Gln	Ile	Thr	Thr	Val	Ser	Gly	Asn
				155					160					165
Glu	Phe	Leu	Leu	Gln	Ser	Asp	Ile	Asp	Phe	Ile	Ile	Leu	Asp	Trp
				170					175					180
Phe	His	Ala	Ile	Lys	Asn	Ala	Ile	Asp	Arg	Leu	Pro	Lys	Asp	Ser
				185					190					195
Ser	Cys	Pro	Ser	Arg	Asn	Leu	Glu	Leu	Phe	Lys	Ile	Gln	Arg	Ser
				200					205					210
Ser	Ser	Thr	Glu	Leu	Leu	Ser	His	Tyr	Asp	Ser	Asp	Ile	Lys	Glu
				215					220					225
Gln	Lys	Pro	Glu	His	Arg	Lys	Ser	Leu	Met	Phe	Arg	Leu	His	His
				230					235					240
Ser	Ala	Ser	Asp	Thr	Ser	Asp	Lys	Asn	Arg	Val	Lys	Ser	Arg	Leu
				245					250					255
Lys	Lys	Phe	Ile	Thr	Arg	Arg	Pro	Ser	Leu	Lys	Thr	Leu	Gln	Glu
				260					265					270
Lys	Gly	Leu	Ile	Lys	Asp	Gln	Ile	Phe	Gly	Ser	His	Leu	His	Lys
				275					280					285
Val	Cys	Glu	Arg	Glu	Asn	Ser	Thr	Val	Pro	Trp	Phe	Val	Lys	Gln
				290					295					300
Cys	Ile	Glu	Ala	Val	Glu	Lys	Arg	Gly	Leu	Asp	Val	Asp	Gly	Ile
				305					310					315
Tyr	Arg	Val	Ser	Gly	Asn	Leu	Ala	Thr	Ile	Gln	Lys	Leu	Arg	Phe
				320					325					330
Ile	Val	Asn	Gln	Glu	Glu	Lys	Leu	Asn	Leu	Asp	Asp	Ser	Gln	Trp
				335					340					345
Glu	Asp	Ile	His	Val	Val	Thr	Gly	Ala	Leu	Lys	Met	Phe	Phe	Arg

Glu	Leu	Pro	Glu	Pro	Leu	Phe	Pro	Tyr	Ser	Phe	Phe	Glu	Gln	Phe	350	355	360
															365	370	375
Val	Glu	Ala	Ile	Lys	Lys	Gln	Asp	Asn	Asn	Thr	Arg	Ile	Glu	Ala	380	385	390
Val	Lys	Ser	Leu	Val	Gln	Lys	Leu	Pro	Pro	Pro	Asn	Arg	Asp	Thr	395	400	405
Met	Lys	Val	Leu	Phe	Gly	His	Leu	Thr	Lys	Ile	Val	Ala	Lys	Ala	410	415	420
Ser	Lys	Asn	Leu	Met	Ser	Thr	Gln	Ser	Leu	Gly	Ile	Val	Phe	Gly	425	430	435
Pro	Thr	Leu	Leu	Arg	Ala	Glu	Asn	Glu	Thr	Gly	Asn	Met	Ala	Ile	440	445	450
His	Met	Val	Tyr	Gln	Asn	Gln	Ile	Ala	Glu	Leu	Met	Leu	Ser	Glu	455	460	465
Tyr	Ser	Lys	Ile	Phe	Gly	Ser	Glu	Glu	Asp						470	475	

<210> 20

<211> 368

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 129023CD1

<400> 20

Met	Ala	Asn	Glu	Asn	His	Gly	Ser	Pro	Arg	Glu	Glu	Ala	Ser	Leu	1	5	10	15
Leu	Ser	His	Ser	Pro	Gly	Thr	Ser	Asn	Gln	Ser	Gln	Pro	Cys	Ser	20	25	30	35
Pro	Lys	Pro	Ile	Arg	Leu	Val	Gln	Asp	Leu	Pro	Glu	Glu	Leu	Val	40	45	50	55
His	Ala	Gly	Trp	Glu	Lys	Cys	Trp	Ser	Arg	Arg	Glu	Asn	Arg	Pro	60	65	70	75
Tyr	Tyr	Phe	Asn	Arg	Phe	Thr	Asn	Gln	Ser	Leu	Trp	Glu	Met	Pro	80	85	90	95
Val	Leu	Gly	Gln	His	Asp	Val	Ile	Ser	Asp	Pro	Leu	Gly	Leu	Asn	100	105	110	115
Ala	Thr	Pro	Leu	Pro	Gln	Asp	Ser	Ser	Leu	Val	Glu	Thr	Pro	Pro	120	125	130	135
Ala	Glu	Asn	Lys	Pro	Arg	Lys	Arg	Gln	Leu	Ser	Glu	Glu	Gln	Pro	140	145	150	155
Ser	Gly	Asn	Gly	Val	Lys	Lys	Pro	Lys	Ile	Glu	Ile	Pro	Val	Thr	160	165	170	175
Pro	Thr	Gly	Gln	Ser	Val	Pro	Ser	Ser	Pro	Ser	Ile	Pro	Gly	Thr	180	185	190	195
Pro	Thr	Leu	Lys	Met	Trp	Gly	Thr	Ser	Pro	Glu	Asp	Lys	Gln	Gln	200	205	210	215
Ala	Ala	Leu	Leu	Arg	Pro	Thr	Glu	Val	Tyr	Trp	Asp	Leu	Asp	Ile	220	225	230	235
Gln	Thr	Asn	Ala	Val	Ile	Lys	His	Arg	Gly	Pro	Ser	Glu	Val	Leu	240	245	250	255
Pro	Pro	His	Pro	Glu	Val	Glu	Leu	Leu	Arg	Ser	Gln	Leu	Ile	Leu	260	265	270	275
Lys	Leu	Arg	Gln	His	Tyr	Arg	Glu	Leu	Cys	Gln	Gln	Arg	Glu	Gly	280	285	290	295
Ile	Glu	Pro	Pro	Arg	Glu	Ser	Phe	Asn	Arg	Trp	Met	Leu	Glu	Arg				
Lys	Val	Val	Asp	Lys	Gly	Ser	Asp	Pro	Leu	Leu	Pro	Ser	Asn	Cys				
Glu	Pro	Val	Val	Ser	Pro	Ser	Met	Phe	Arg	Glu	Ile	Met	Asn	Asp				
Ile	Pro	Ile	Arg	Leu	Ser	Arg	Ile	Lys	Phe	Arg	Glu	Glu	Ala	Lys				
Arg	Leu	Leu	Phe	Lys	Tyr	Ala	Glu	Ala	Ala	Arg	Arg	Leu	Ile	Glu				

	350		355		360
Phe Gln Glu Val	Glu Asn Phe Phe Thr	Phe Leu Lys Asn Ile	Asn		
	365		370		375
Asp Val Asp Thr	Ala Leu Ser Phe Tyr	His Met Ala Gly Ala	Ser		
	380		385		390
Leu Asp Lys Val	Thr Met Gln Gln Val	Ala Arg Thr Val Ala	Lys		
	395		400		405
Val Glu Leu Ser	Asp His Val Cys Asp	Val Val Phe Ala Leu	Phe		
	410		415		420
Asp Cys Asp Gly	Asn Gly Glu Leu Ser	Asn Lys Glu Phe Val	Ser		
	425		430		435
Ile Met Lys Gln	Arg Leu Met Arg Gly	Leu Glu Lys Pro Lys	Asp		
	440		445		450
Met Gly Phe Thr	Arg Leu Met Gln Ala	Met Trp Lys Cys Ala	Gln		
	455		460		465
Glu Thr Ala Trp	Asp Phe Ala Leu Pro	Lys Gln			
	470		475		

<210> 22

<211> 171

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1682320CD1

<400> 22

Met Glu Lys Arg	Leu Gln Glu Ala Gln	Leu Tyr Lys Glu Glu Gly	
1	5	10	15
Asn Gln Arg Tyr	Arg Glu Gly Lys Tyr	Arg Asp Ala Val Ser Arg	
	20	25	30
Tyr His Arg Ala	Leu Gln Leu Arg	Gly Leu Asp Pro Ser Leu	
	35	40	45
Pro Ser Pro Leu	Pro Asn Leu Gly Pro	Gln Gly Pro Ala Leu Thr	
	50	55	60
Pro Glu Gln Glu	Asn Ile Leu His Thr	Thr Gln Thr Asp Cys Tyr	
	65	70	75
Asn Asn Leu Ala	Ala Cys Leu Leu Gln	Met Glu Pro Val Asn Tyr	
	80	85	90
Glu Arg Val Arg	Glu Tyr Ser Gln Lys	Val Leu Glu Arg Gln Pro	
	95	100	105
Asp Asn Ala Lys	Ala Leu Tyr Arg Ala	Gly Val Ala Phe Phe His	
	110	115	120
Leu Gln Asp Tyr	Asp Gln Ala Arg His	Tyr Leu Leu Ala Ala Val	
	125	130	135
Asn Arg Gln Pro	Lys Asp Ala Asn Val	Arg Arg Tyr Leu Gln Leu	
	140	145	150
Thr Gln Ser Glu	Leu Ser Ser Tyr His	Arg Lys Glu Lys Gln Leu	
	155	160	165
Tyr Leu Gly Met	Phe Gly		
	170		

<210> 23

<211> 163

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1728263CD1

<400> 23

Met Phe Phe Ser	Glu Ala Arg Ala Arg	Ser Arg Thr Trp Glu Ala	
1	5	10	15
Ser Pro Ser Glu	His Arg Lys Trp Val	Glu Val Phe Lys Ala Cys	
	20	25	30
Asp Glu Asp His	Lys Gly Tyr Leu Ser	Arg Glu Asp Phe Lys Thr	
	35	40	45

Ala	Val	Val	Met	Leu	Phe	Gly	Tyr	Lys	Pro	Ser	Lys	Ile	Glu	Val	
				50					55					60	
Asp	Ser	Val	Met	Ser	Ser	Ile	Asn	Pro	Asn	Thr	Ser	Gly	Ile	Leu	
				65					70					75	
Leu	Glu	Gly	Phe	Leu	Asn	Ile	Val	Arg	Lys	Lys	Lys	Glu	Ala	Gln	
				80					85					90	
Arg	Tyr	Arg	Asn	Glu	Val	Arg	His	Ile	Phe	Thr	Ala	Phe	Asp	Thr	
				95					100					105	
Tyr	Tyr	Arg	Gly	Phe	Leu	Thr	Leu	Glu	Asp	Phe	Lys	Lys	Ala	Phe	
				110					115					120	
Arg	Gln	Val	Ala	Pro	Lys	Leu	Pro	Glu	Arg	Thr	Val	Leu	Glu	Val	
				125					130					135	
Phe	Arg	Glu	Val	Asp	Arg	Asp	Ser	Asp	Gly	His	Val	Ser	Phe	Arg	
				140					145					150	
Asp	Phe	Glu	Tyr	Ala	Leu	Asn	Tyr	Gly	Gln	Lys	Glu	Ala			
				155					160						

<210> 24

<211> 354

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1867626CD1

<400> 24

Met	Gly	Glu	Gln	Pro	Ile	Phe	Ser	Thr	Arg	Ala	His	Val	Phe	Gln	
1				5					10					15	
Ile	Asp	Pro	Asn	Thr	Lys	Lys	Asn	Trp	Val	Pro	Thr	Ser	Lys	His	
				20					25					30	
Ala	Val	Thr	Val	Ser	Tyr	Phe	Tyr	Asp	Ser	Thr	Arg	Asn	Val	Tyr	
				35					40					45	
Arg	Ile	Ile	Ser	Leu	Asp	Gly	Ser	Lys	Ala	Ile	Ile	Asn	Ser	Thr	
				50					55					60	
Ile	Thr	Pro	Asn	Met	Thr	Phe	Thr	Lys	Thr	Ser	Gln	Arg	Phe	Gly	
				65					70					75	
Gln	Trp	Ala	Asp	Ser	Arg	Ala	Asn	Thr	Val	Tyr	Gly	Leu	Gly	Phe	
				80					85					90	
Ser	Ser	Glu	His	His	Leu	Ser	Lys	Phe	Ala	Glu	Lys	Phe	Gln	Glu	
				95					100					105	
Phe	Lys	Glu	Ala	Ala	Arg	Leu	Ala	Lys	Glu	Lys	Ser	Gln	Glu	Lys	
				110					115					120	
Met	Glu	Leu	Thr	Ser	Thr	Pro	Ser	Gln	Glu	Ser	Ala	Gly	Gly	Asp	
				125					130					135	
Leu	Gln	Ser	Pro	Leu	Thr	Pro	Glu	Ser	Ile	Asn	Gly	Thr	Asp	Asp	
				140					145					150	
Glu	Arg	Thr	Pro	Asp	Val	Thr	Gln	Asn	Ser	Glu	Pro	Arg	Ala	Glu	
				155					160					165	
Pro	Thr	Gln	Asn	Ala	Leu	Pro	Phe	Ser	His	Ser	Ser	Ala	Ile	Ser	
				170					175					180	
Lys	His	Trp	Glu	Ala	Glu	Leu	Ala	Thr	Leu	Lys	Gly	Asn	Asn	Ala	
				185					190					195	
Lys	Leu	Thr	Ala	Ala	Leu	Leu	Glu	Ser	Thr	Ala	Asn	Val	Lys	Gln	
				200					205					210	
Trp	Lys	Gln	Gln	Leu	Ala	Ala	Tyr	Gln	Glu	Glu	Ala	Glu	Arg	Leu	
				215					220					225	
His	Lys	Arg	Val	Thr	Glu	Leu	Glu	Cys	Val	Ser	Ser	Gln	Ala	Asn	
				230					235					240	
Ala	Val	His	Thr	His	Lys	Thr	Glu	Leu	Asn	Gln	Thr	Ile	Gln	Glu	
				245					250					255	
Leu	Glu	Glu	Thr	Leu	Lys	Leu	Lys	Glu	Glu	Glu	Ile	Glu	Arg	Leu	
				260					265					270	
Lys	Gln	Glu	Ile	Asp	Asn	Ala	Arg	Glu	Leu	Gln	Glu	Gln	Arg	Asp	
				275					280					285	
Ser	Leu	Thr	Gln	Lys	Leu	Gln	Glu	Val	Glu	Ile	Arg	Asn	Lys	Asp	
				290					295					300	
Leu	Glu	Gly	Gln	Leu	Ser	Asp	Leu	Glu	Gln	Arg	Leu	Glu	Lys	Ser	

	305		310		315
Gln Asn Glu Gln	Glu Ala Phe Arg Asn	Asn Leu Lys Thr Leu	Leu		
	320		325		330
Glu Ile Leu Asp	Gly Lys Ile Phe Glu	Leu Thr Glu Leu Arg	Asp		
	335		340		345
Asn Leu Ala Lys	Leu Leu Glu Cys Ser				
	350				

<210> 25

<211> 365

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1990126CD1

<400> 25

Met Asn Ile Met Asp	Phe Asn Val Lys Lys	Leu Ala Ala Asp Ala	
1	5	10	15
Gly Thr Phe Leu Ser	Arg Ala Val Gln Phe	Thr Glu Glu Lys Leu	
	20	25	30
Gly Gln Ala Glu Lys	Thr Glu Leu Asp Ala	His Leu Glu Asn Leu	
	35	40	45
Leu Ser Lys Ala Glu	Cys Thr Lys Ile Trp	Thr Glu Lys Ile Met	
	50	55	60
Lys Gln Thr Glu Val	Leu Leu Gln Pro Asn	Pro Asn Ala Arg Ile	
	65	70	75
Glu Glu Phe Val Tyr	Glu Lys Leu Asp Arg	Lys Ala Pro Ser Arg	
	80	85	90
Ile Asn Asn Pro Glu	Leu Leu Gly Gln Tyr	Met Ile Asp Ala Gly	
	95	100	105
Thr Glu Phe Gly Pro	Gly Thr Ala Tyr Gly	Asn Ala Leu Ile Lys	
	110	115	120
Cys Gly Glu Thr Gln	Lys Arg Ile Gly Thr	Ala Asp Arg Glu Leu	
	125	130	135
Ile Gln Thr Ser Ala	Leu Asn Phe Leu Thr	Pro Leu Arg Asn Phe	
	140	145	150
Ile Glu Gly Asp Tyr	Lys Thr Ile Ala Lys	Glu Arg Lys Leu Leu	
	155	160	165
Gln Asn Lys Arg Leu	Asp Leu Asp Ala Lys	Thr Arg Leu Lys	
	170	175	180
Lys Ala Lys Ala Ala	Glu Thr Arg Asn Ser	Ser Glu Gln Glu Leu	
	185	190	195
Arg Ile Thr Gln Ser	Glu Phe Asp Arg Gln	Ala Glu Ile Thr Arg	
	200	205	210
Leu Leu Leu Glu Gly	Ile Ser Ser Thr His	Ala His His Leu Arg	
	215	220	225
Cys Leu Asn Asp Phe	Val Glu Ala Gln Met	Thr Tyr Tyr Ala Gln	
	230	235	240
Cys Tyr Gln Tyr Met	Leu Asp Leu Gln Lys	Gln Leu Gly Ser Phe	
	245	250	255
Pro Ser Asn Tyr Leu	Ser Asn Asn Asn Gln	Thr Ser Val Thr Pro	
	260	265	270
Val Pro Ser Val Leu	Pro Asn Ala Ile Gly	Ser Ser Ala Met Ala	
	275	280	285
Ser Thr Ser Gly Leu	Val Ile Thr Ser Pro	Ser Asn Leu Ser Asp	
	290	295	300
Leu Lys Glu Cys Ser	Gly Ser Arg Lys Ala	Arg Val Leu Tyr Asp	
	305	310	315
Tyr Asp Ala Ala Asn	Ser Thr Glu Leu Ser	Leu Leu Ala Asp Glu	
	320	325	330
Val Ile Thr Val Phe	Ser Val Val Gly Met	Asp Ser Asp Trp Leu	
	335	340	345
Met Gly Glu Arg Gly	Asn Gln Lys Gly Lys	Val Pro Ile Thr Tyr	
	350	355	360
Leu Glu Leu Leu Asn			
	365		

<210> 26
 <211> 274
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2104180CD1

<400> 26
 Met Ala Thr Thr Val Ser Thr Gln Arg Gly Pro Val Tyr Ile Gly
 1 5 10 15
 Glu Leu Pro Gln Asp Phe Leu Arg Ile Thr Pro Thr Gln Gln Gln
 20 25 30
 Arg Gln Val Gln Leu Asp Ala Gln Ala Ala Gln Gln Leu Gln Tyr
 35 40 45
 Gly Gly Ala Val Gly Thr Val Gly Arg Leu Asn Ile Thr Val Val
 50 55 60
 Gln Ala Lys Leu Ala Lys Asn Tyr Gly Met Thr Arg Met Asp Pro
 65 70 75
 Tyr Cys Arg Leu Arg Leu Gly Tyr Ala Val Tyr Glu Thr Pro Thr
 80 85 90
 Ala His Asn Gly Ala Lys Asn Pro Arg Trp Asn Lys Val Ile His
 95 100 105
 Cys Thr Val Pro Pro Gly Val Asp Ser Phe Tyr Leu Glu Ile Phe
 110 115 120
 Asp Glu Arg Ala Phe Ser Met Asp Asp Arg Ile Ala Trp Thr His
 125 130 135
 Ile Thr Ile Pro Glu Ser Leu Arg Gln Gly Lys Val Glu Asp Lys
 140 145 150
 Trp Tyr Ser Leu Ser Gly Arg Gln Gly Asp Asp Lys Glu Gly Met
 155 160 165
 Ile Asn Leu Val Met Ser Tyr Ala Leu Leu Pro Ala Ala Met Val
 170 175 180
 Met Pro Pro Gln Pro Val Val Leu Met Pro Thr Val Tyr Gln Gln
 185 190 195
 Gly Val Gly Tyr Val Pro Ile Thr Gly Met Pro Ala Val Cys Ser
 200 205 210
 Pro Gly Met Val Pro Val Ala Leu Pro Pro Ala Ala Val Asn Ala
 215 220 225
 Gln Pro Arg Cys Ser Glu Glu Asp Leu Lys Ala Ile Gln Asp Met
 230 235 240
 Phe Pro Asn Met Asp Gln Glu Val Ile Arg Ser Val Leu Glu Ala
 245 250 255
 Gln Arg Gly Asn Lys Asp Ala Ala Ile Asn Ser Leu Leu Gln Met
 260 265 270
 Gly Glu Glu Pro

<210> 27
 <211> 129
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2122241CD1

<400> 27
 Met Arg Arg Arg Gly Glu Ile Asp Met Ala Thr Glu Gly Asp Val
 1 5 10 15
 Glu Leu Glu Leu Glu Thr Glu Thr Ser Gly Pro Glu Arg Pro Pro
 20 25 30
 Glu Lys Pro Arg Lys His Asp Ser Gly Ala Ala Asp Leu Glu Arg
 35 40 45
 Val Thr Asp Tyr Ala Glu Glu Lys Glu Ile Gln Ser Ser Asn Leu
 50 55 60
 Glu Thr Ala Met Ser Val Ile Gly Asp Arg Arg Ser Arg Glu Gln

	65		70		75									
Lys	Ala	Lys	Gln	Glu	Arg	Glu	Lys	Glu	Leu	Ala	Lys	Val	Thr	Ile
	80								85					90
Lys	Lys	Glu	Asp	Leu	Glu	Leu	Ile	Met	Thr	Glu	Met	Glu	Ile	Ser
	95								100					105
Arg	Ala	Ala	Ala	Glu	Arg	Ser	Leu	Arg	Glu	His	Met	Gly	Asn	Val
	110								115					120
Val	Glu	Ala	Leu	Ile	Ala	Leu	Thr	Asn						
	125													

<210> 28

<211> 626

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2580428CD1

<400> 28

Met	Gln	Arg	Ala	Asp	Ser	Glu	Gln	Pro	Ser	Lys	Arg	Pro	Arg	Cys
1				5					10					15
Asp	Asp	Ser	Pro	Arg	Thr	Pro	Ser	Asn	Thr	Pro	Ser	Ala	Glu	Ala
				20					25					30
Asp	Trp	Ser	Pro	Gly	Leu	Glu	Leu	His	Pro	Asp	Tyr	Lys	Thr	Trp
				35					40					45
Gly	Pro	Glu	Gln	Val	Cys	Ser	Phe	Leu	Arg	Arg	Gly	Gly	Phe	Glu
				50					55					60
Glu	Pro	Val	Leu	Leu	Lys	Asn	Ile	Arg	Glu	Asn	Glu	Ile	Thr	Gly
				65					70					75
Ala	Leu	Leu	Pro	Cys	Leu	Asp	Glu	Ser	Arg	Phe	Glu	Asn	Leu	Gly
				80					85					90
Val	Ser	Ser	Leu	Gly	Glu	Arg	Lys	Lys	Leu	Leu	Ser	Tyr	Ile	Gln
				95					100					105
Arg	Leu	Val	Gln	Ile	His	Val	Asp	Thr	Met	Lys	Val	Ile	Asn	Asp
				110					115					120
Pro	Ile	His	Gly	His	Ile	Glu	Leu	His	Pro	Leu	Leu	Val	Arg	Ile
				125					130					135
Ile	Asp	Thr	Pro	Gln	Phe	Gln	Arg	Leu	Arg	Tyr	Ile	Lys	Gln	Leu
				140					145					150
Gly	Gly	Gly	Tyr	Tyr	Val	Phe	Pro	Gly	Ala	Ser	His	Asn	Arg	Phe
				155					160					165
Glu	His	Ser	Leu	Gly	Val	Gly	Tyr	Leu	Ala	Gly	Cys	Leu	Val	His
				170					175					180
Ala	Leu	Gly	Glu	Lys	Gln	Pro	Glu	Leu	Gln	Ile	Ser	Glu	Arg	Asp
				185					190					195
Val	Leu	Cys	Val	Gln	Ile	Ala	Gly	Leu	Cys	His	Asp	Leu	Gly	His
				200					205					210
Gly	Pro	Phe	Ser	His	Met	Phe	Asp	Gly	Arg	Phe	Ile	Pro	Leu	Ala
				215					220					225
Arg	Pro	Glu	Val	Lys	Trp	Thr	His	Glu	Gln	Gly	Ser	Val	Met	Met
				230					235					240
Phe	Glu	His	Leu	Ile	Asn	Ser	Asn	Gly	Ile	Lys	Pro	Val	Met	Glu
				245					250					255
Gln	Tyr	Gly	Leu	Ile	Pro	Glu	Glu	Asp	Ile	Cys	Phe	Ile	Lys	Glu
				260					265					270
Gln	Ile	Val	Gly	Pro	Leu	Glu	Ser	Pro	Val	Glu	Asp	Ser	Leu	Trp
				275					280					285
Pro	Tyr	Lys	Gly	Arg	Pro	Glu	Asn	Lys	Ser	Phe	Leu	Tyr	Glu	Ile
				290					295					300
Val	Ser	Asn	Lys	Arg	Asn	Gly	Ile	Asp	Val	Asp	Lys	Trp	Asp	Tyr
				305					310					315
Phe	Ala	Arg	Asp	Cys	His	His	Leu	Gly	Ile	Gln	Asn	Asn	Phe	Asp
				320					325					330
Tyr	Lys	Arg	Phe	Ile	Lys	Phe	Ala	Arg	Val	Cys	Glu	Val	Asp	Asn
				335					340					345
Glu	Leu	Arg	Ile	Cys	Ala	Arg	Asp	Lys	Glu	Val	Gly	Asn	Leu	Tyr
				350					355					360

Asp	Met	Phe	His	Thr	Arg	Asn	Ser	Leu	His	Arg	Arg	Ala	Tyr	Gln
				365					370					375
His	Lys	Val	Gly	Asn	Ile	Ile	Asp	Thr	Met	Ile	Thr	Asp	Ala	Phe
				380					385					390
Leu	Lys	Ala	Asp	Asp	Tyr	Ile	Glu	Ile	Thr	Gly	Ala	Gly	Gly	Lys
				395					400					405
Lys	Tyr	Arg	Ile	Ser	Thr	Ala	Ile	Asp	Asp	Met	Glu	Ala	Tyr	Thr
				410					415					420
Lys	Leu	Thr	Asp	Asn	Ile	Phe	Leu	Glu	Ile	Leu	Tyr	Ser	Thr	Asp
				425					430					435
Pro	Lys	Leu	Lys	Asp	Ala	Arg	Glu	Ile	Leu	Lys	Gln	Ile	Glu	Tyr
				440					445					450
Arg	Asn	Leu	Phe	Lys	Tyr	Val	Gly	Glu	Thr	Gln	Pro	Thr	Gly	Gln
				455					460					465
Ile	Lys	Ile	Lys	Arg	Glu	Asp	Tyr	Glu	Ser	Leu	Pro	Lys	Glu	Val
				470					475					480
Ala	Ser	Ala	Lys	Pro	Lys	Val	Leu	Leu	Asp	Val	Lys	Leu	Lys	Ala
				485					490					495
Glu	Asp	Phe	Ile	Val	Asp	Val	Ile	Asn	Met	Asp	Tyr	Gly	Met	Gln
				500					505					510
Glu	Lys	Asn	Pro	Ile	Asp	His	Val	Ser	Phe	Tyr	Cys	Lys	Thr	Ala
				515					520					525
Pro	Asn	Arg	Ala	Ile	Arg	Ile	Thr	Lys	Asn	Gln	Val	Ser	Gln	Leu
				530					535					540
Leu	Pro	Glu	Lys	Phe	Ala	Glu	Gln	Leu	Ile	Arg	Val	Tyr	Cys	Lys
				545					550					555
Lys	Val	Asp	Arg	Lys	Ser	Leu	Tyr	Ala	Ala	Arg	Gln	Tyr	Phe	Val
				560					565					570
Gln	Trp	Cys	Ala	Asp	Arg	Asn	Phe	Thr	Lys	Pro	Gln	Asp	Gly	Asp
				575					580					585
Val	Ile	Ala	Pro	Leu	Ile	Thr	Pro	Gln	Lys	Lys	Glu	Trp	Asn	Asp
				590					595					600
Ser	Thr	Ser	Val	Gln	Asn	Pro	Thr	Arg	Leu	Arg	Glu	Ala	Ser	Lys
				605					610					615
Ser	Arg	Val	Gln	Leu	Phe	Lys	Asp	Asp	Pro	Met				
				620					625					

<210> 29

<211> 157

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3397189CD1

<400> 29

Met	Ala	Pro	Lys	Lys	Leu	Ser	Cys	Leu	Arg	Ser	Leu	Leu	Leu	Pro
1				5					10					15
Leu	Ser	Leu	Thr	Leu	Leu	Leu	Pro	Gln	Ala	Asp	Thr	Arg	Ser	Phe
				20					25					30
Val	Val	Asp	Arg	Gly	His	Asp	Arg	Phe	Leu	Leu	Asp	Gly	Ala	Pro
				35					40					45
Phe	Arg	Tyr	Val	Ser	Gly	Ser	Leu	His	Tyr	Phe	Arg	Val	Pro	Arg
				50					55					60
Val	Leu	Trp	Ala	Asp	Arg	Leu	Leu	Lys	Met	Arg	Trp	Ser	Gly	Leu
				65					70					75
Asn	Ala	Ile	Gln	Phe	Tyr	Val	Pro	Trp	Asn	Tyr	His	Glu	Pro	Gln
				80					85					90
Pro	Gly	Val	Tyr	Asn	Phe	Asn	Gly	Ser	Arg	Asp	Leu	Ile	Ala	Phe
				95					100					105
Leu	Asn	Glu	Ala	Ala	Leu	Ala	Asn	Leu	Leu	Val	Ile	Leu	Arg	Pro
				110					115					120
Gly	Pro	Tyr	Ile	Cys	Ala	Glu	Trp	Glu	Met	Gly	Gly	Leu	Pro	Ser
				125					130					135
Trp	Leu	Leu	Arg	Lys	Pro	Glu	Ile	His	Leu	Arg	Thr	Ser	Asp	Pro
				140					145					150
Gly	Glu	Leu	Arg	Gln	Arg	Ile								

155

<210> 30
 <211> 383
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <223> Incyte ID No: 4881249CD1

<400> 30
 Met Leu Ser Arg Lys Lys Thr Lys Asn Glu Val Ser Lys Pro Ala
 1 5 10 15
 Glu Val Gln Gly Lys Tyr Val Lys Lys Glu Thr Ser Pro Leu Leu
 20 25 30
 Arg Asn Leu Met Pro Ser Phe Ile Arg His Gly Pro Thr Ile Pro
 35 40 45
 Arg Arg Thr Asp Ile Cys Leu Pro Asp Ser Ser Pro Asn Ala Phe
 50 55 60
 Ser Thr Ser Gly Asp Val Val Ser Arg Asn Gln Ser Phe Leu Arg
 65 70 75
 Thr Pro Ile Gln Arg Thr Pro His Glu Ile Met Arg Arg Glu Ser
 80 85 90
 Asn Arg Leu Ser Ala Pro Ser Tyr Leu Ala Arg Ser Leu Ala Asp
 95 100 105
 Val Pro Arg Glu Tyr Gly Ser Ser Gln Ser Phe Val Thr Glu Val
 110 115 120
 Ser Phe Ala Val Glu Asn Gly Asp Ser Gly Ser Arg Tyr Tyr Tyr
 125 130 135
 Ser Asp Asn Phe Phe Asp Gly Gln Arg Lys Arg Pro Leu Gly Asp
 140 145 150
 Arg Ala His Glu Asp Tyr Arg Tyr Tyr Glu Tyr Asn His Asp Leu
 155 160 165
 Phe Gln Arg Met Pro Gln Asn Gln Gly Arg His Ala Ser Gly Ile
 170 175 180
 Gly Arg Val Ala Ala Thr Ser Leu Gly Asn Leu Thr Asn His Gly
 185 190 195
 Ser Glu Asp Leu Pro Leu Pro Pro Gly Trp Ser Val Asp Trp Thr
 200 205 210
 Met Arg Gly Arg Lys Tyr Tyr Ile Asp His Asn Thr Asn Thr Thr
 215 220 225
 His Trp Ser His Pro Leu Glu Arg Glu Gly Leu Pro Pro Gly Trp
 230 235 240
 Glu Arg Val Glu Ser Ser Glu Phe Gly Thr Tyr Tyr Val Asp His
 245 250 255
 Thr Asn Lys Lys Ala Gln Tyr Arg His Pro Cys Ala Pro Ser Val
 260 265 270
 Pro Arg Tyr Asp Gln Pro Pro Pro Val Thr Tyr Gln Pro Gln Gln
 275 280 285
 Thr Glu Arg Asn Gln Ser Leu Leu Val Pro Ala Asn Pro Tyr His
 290 295 300
 Thr Ala Glu Ile Pro Asp Trp Leu Gln Val Tyr Ala Arg Ala Pro
 305 310 315
 Val Lys Tyr Asp His Ile Leu Lys Trp Glu Leu Phe Gln Leu Ala
 320 325 330
 Asp Leu Asp Thr Tyr Gln Gly Met Leu Lys Leu Leu Phe Met Lys
 335 340 345
 Glu Leu Glu Gln Ile Val Lys Met Tyr Glu Ala Tyr Arg Gln Ala
 350 355 360
 Leu Leu Thr Glu Leu Glu Asn Arg Lys Gln Arg Gln Gln Trp Tyr
 365 370 375
 Ala Gln Gln His Gly Lys Asn Phe
 380

<210> 31
 <211> 478
 <212> PRT
 <213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 431871CD1

<400> 31

Met	Asp	Thr	Ser	Asp	Leu	Phe	Ala	Ser	Cys	Arg	Lys	Gly	Asp	Val
1				5					10					15
Gly	Arg	Val	Arg	Tyr	Leu	Leu	Glu	Gln	Arg	Asp	Val	Glu	Val	Asn
				20					25					30
Val	Arg	Asp	Lys	Trp	Asp	Ser	Thr	Pro	Leu	Tyr	Tyr	Ala	Cys	Leu
				35					40					45
Cys	Gly	His	Glu	Glu	Leu	Val	Leu	Tyr	Leu	Leu	Ala	Asn	Gly	Ala
				50					55					60
Arg	Cys	Glu	Ala	Asn	Thr	Phe	Asp	Gly	Glu	Arg	Cys	Leu	Tyr	Gly
				65					70					75
Ala	Leu	Ser	Asp	Pro	Ile	Arg	Arg	Ala	Leu	Arg	Asp	Tyr	Lys	Gln
				80					85					90
Val	Thr	Ala	Ser	Cys	Arg	Arg	Arg	Asp	Tyr	Tyr	Asp	Asp	Phe	Leu
				95					100					105
Gln	Arg	Leu	Leu	Glu	Gln	Gly	Ile	His	Ser	Asp	Val	Val	Phe	Val
				110					115					120
Val	His	Gly	Lys	Pro	Phe	Arg	Val	His	Arg	Cys	Val	Leu	Gly	Ala
				125					130					135
Arg	Ser	Ala	Tyr	Phe	Ala	Asn	Met	Leu	Asp	Thr	Lys	Trp	Lys	Gly
				140					145					150
Lys	Ser	Val	Val	Val	Leu	Arg	His	Pro	Leu	Ile	Asn	Pro	Val	Ala
				155					160					165
Phe	Gly	Ala	Leu	Leu	Gln	Tyr	Leu	Tyr	Thr	Gly	Arg	Leu	Asp	Ile
				170					175					180
Gly	Val	Glu	His	Val	Ser	Asp	Cys	Glu	Arg	Leu	Ala	Lys	Gln	Cys
				185					190					195
Gln	Leu	Trp	Asp	Leu	Leu	Ser	Asp	Leu	Glu	Ala	Lys	Cys	Glu	Lys
				200					205					210
Val	Ser	Glu	Phe	Val	Ala	Ser	Lys	Pro	Gly	Thr	Cys	Val	Lys	Val
				215					220					225
Leu	Thr	Ile	Glu	Pro	Pro	Pro	Ala	Asp	Pro	Arg	Leu	Arg	Glu	Asp
				230					235					240
Met	Ala	Leu	Leu	Ala	Asp	Cys	Ala	Leu	Pro	Pro	Glu	Leu	Arg	Gly
				245					250					255
Asp	Leu	Trp	Glu	Leu	Pro	Phe	Pro	Cys	Pro	Asp	Gly	Phe	Asn	Ser
				260					265					270
Cys	Pro	Asp	Ile	Cys	Phe	Arg	Val	Ala	Gly	Cys	Ser	Phe	Leu	Cys
				275					280					285
His	Lys	Ala	Phe	Phe	Cys	Gly	Arg	Ser	Asp	Tyr	Phe	Arg	Ala	Leu
				290					295					300
Leu	Asp	Asp	His	Phe	Arg	Glu	Ser	Glu	Glu	Pro	Ala	Thr	Ser	Gly
				305					310					315
Gly	Pro	Pro	Ala	Val	Thr	Leu	His	Gly	Ile	Ser	Pro	Asp	Val	Phe
				320					325					330
Thr	His	Val	Leu	Tyr	Tyr	Met	Tyr	Ser	Asp	His	Thr	Glu	Leu	Ser
				335					340					345
Pro	Glu	Ala	Ala	Tyr	Asp	Val	Leu	Ser	Val	Ala	Asp	Met	Tyr	Leu
				350					355					360
Leu	Pro	Gly	Leu	Lys	Arg	Leu	Cys	Gly	Arg	Ser	Leu	Ala	Gln	Met
				365					370					375
Leu	Asp	Glu	Asp	Thr	Val	Val	Gly	Val	Trp	Arg	Val	Ala	Lys	Leu
				380					385					390
Phe	Arg	Leu	Ala	Arg	Leu	Glu	Asp	Gln	Cys	Thr	Glu	Tyr	Met	Ala
				395					400					405
Lys	Val	Ile	Glu	Lys	Leu	Val	Glu	Arg	Glu	Asp	Phe	Val	Glu	Ala
				410					415					420
Val	Lys	Glu	Glu	Ala	Ala	Ala	Val	Ala	Ala	Arg	Gln	Glu	Thr	Asp
				425					430					435
Ser	Ile	Pro	Leu	Val	Asp	Asp	Ile	Arg	Phe	His	Val	Ala	Ser	Thr
				440					445					450
Val	Gln	Thr	Tyr	Ser	Ala	Ile	Glu	Glu	Ala	Gln	Gln	Arg	Leu	Arg
				455					460					465

Ala Leu Glu Asp Leu Leu Val Ser Ile Gly Leu Asp Cys
 470 475

<210> 32
 <211> 275
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 526155CD1

<400> 32
 Met Ser Ala Glu Val Lys Val Thr Gly Gln Asn Gln Glu Gln Phe
 1 5 10 15
 Leu Leu Leu Ala Lys Ser Ala Lys Gly Ala Ala Leu Ala Thr Leu
 20 25 30
 Ile His Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu
 35 40 45
 Leu Leu Asp Met Pro Asn Val Arg Glu Leu Ala Glu Ser Asp Phe
 50 55 60
 Ala Ser Thr Phe Arg Leu Leu Thr Val Phe Ala Tyr Gly Thr Tyr
 65 70 75
 Ala Asp Tyr Leu Ala Glu Ala Arg Asn Leu Pro Pro Leu Thr Glu
 80 85 90
 Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala
 95 100 105
 Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu
 110 115 120
 Ala Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala
 125 130 135
 Val Tyr Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln
 140 145 150
 Arg Leu Glu Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln
 155 160 165
 Asp Leu Ser Ala Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly
 170 175 180
 Cys Glu Val Val Leu Ser Gly Ile Glu Glu Gln Val Ser Arg Ala
 185 190 195
 Asn Gln His Lys Glu Gln Gln Leu Gly Leu Lys Gln Gln Ile Glu
 200 205 210
 Ser Glu Val Ala Asn Leu Lys Lys Thr Ile Lys Val Thr Thr Ala
 215 220 225
 Ala Ala Ala Ala Ala Thr Ser Gln Asp Pro Glu Gln His Leu Thr
 230 235 240
 Glu Leu Arg Glu Pro Ala Pro Gly Thr Asn Gln Arg Gln Pro Ser
 245 250 255
 Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg Gly Ser Ala Lys Ile
 260 265 270
 Trp Ser Lys Ser Asn
 275

<210> 33
 <211> 217
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 676234CD1

<400> 33
 Met Ala Ser Thr Gly Leu Glu Leu Leu Gly Met Thr Leu Ala Val
 1 5 10 15
 Leu Gly Trp Leu Gly Thr Leu Val Ser Cys Ala Leu Pro Leu Trp
 20 25 30
 Lys Val Thr Ala Phe Ile Gly Asn Ser Ile Val Val Ala Gln Val

```

      35      40      45
Val Trp Glu Gly Leu Trp Met Ser Cys Val Val Gln Ser Thr Gly
      50      55      60
Gln Met Gln Cys Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln
      65      70      75
Asp Leu Gln Ala Ala Arg Ala Leu Cys Val Ile Ala Leu Leu Leu
      80      85      90
Ala Leu Leu Gly Leu Leu Val Ala Ile Thr Gly Ala Gln Cys Thr
      95     100     105
Thr Cys Val Glu Asp Glu Gly Ala Lys Ala Arg Ile Val Leu Thr
     110     115     120
Ala Gly Val Ile Leu Leu Leu Ala Gly Ile Leu Val Leu Ile Pro
     125     130     135
Val Cys Trp Thr Ala His Ala Ile Ile Gln Asp Phe Tyr Asn Pro
     140     145     150
Leu Val Ala Glu Ala Leu Lys Arg Glu Leu Gly Ala Ser Leu Tyr
     155     160     165
Leu Gly Trp Ala Ala Ala Ala Leu Leu Met Leu Gly Gly Gly Leu
     170     175     180
Leu Cys Cys Thr Cys Pro Pro Pro Gln Val Glu Arg Pro Arg Gly
     185     190     195
Pro Arg Leu Gly Tyr Ser Ile Pro Ser Arg Ser Gly Ala Ser Gly
     200     205     210
Leu Asp Lys Arg Asp Tyr Val
     215

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<210> 34

<211> 74

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 720145CD1

<400> 34

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Met Asp Asp Tyr Thr Ser Ala Ile Glu Val Gln Pro Asn Phe Glu
  1      5      10      15
Val Pro Tyr Tyr Asn Arg Gly Leu Ile Leu Tyr Arg Leu Gly Tyr
      20      25      30
Phe Asp Asp Ala Leu Glu Asp Phe Lys Lys Val Leu Asp Leu Asn
      35      40      45
Pro Gly Phe Gln Asp Ala Thr Leu Ser Leu Lys Gln Thr Ile Leu
      50      55      60
Asp Lys Glu Glu Lys Gln Arg Arg Asn Val Ala Lys Asn Tyr
      65      70

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<210> 35

<211> 367

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1001951CD1

<400> 35

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Met Val Gln Gln Phe Leu Arg Gln Ala Gln Arg Gly Thr Glu Glu
  1      5      10      15
Lys Glu Arg Glu Gly Ala Leu Val Ser Leu Arg Arg Gly Leu Gln
      20      25      30
His Pro Glu Thr Gln Gln Thr Phe Ile Arg Ser Cys Val Cys Ile
      35      40      45
His Trp Val Thr Leu Ile Val Glu Ser Glu Ala Val Arg Arg Gln
      50      55      60
Leu Leu Pro Gln Gly Ile Val Pro Ala Leu Ala Ala Cys Ile Gln
      65      70      75
Ser Pro His Val Ala Val Leu Glu Ala Leu Gly Tyr Ala Leu Ser
      80      85      90

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Gln	Leu	Leu	Gln	Ala	Glu	Glu	Ala	Pro	Glu	Lys	Ile	Ile	Pro	Ser
				95					100					105
Ile	Leu	Ala	Ser	Thr	Leu	Pro	Gln	His	Met	Leu	Gln	Met	Leu	Gln
				110					115					120
Pro	Gly	Pro	Lys	Leu	Asn	Pro	Gly	Val	Ala	Val	Glu	Phe	Ala	Trp
				125					130					135
Cys	Leu	His	Tyr	Ile	Ile	Cys	Ser	Gln	Val	Ser	Asn	Pro	Leu	Leu
				140					145					150
Ile	Gly	His	Gly	Ala	Leu	Ser	Thr	Leu	Gly	Leu	Leu	Leu	Leu	Asp
				155					160					165
Leu	Ala	Gly	Ala	Val	Gln	Lys	Thr	Glu	Asp	Ala	Gly	Leu	Glu	Leu
				170					175					180
Leu	Ala	Cys	Pro	Val	Leu	Arg	Cys	Leu	Ser	Asn	Leu	Leu	Thr	Glu
				185					190					195
Ala	Ala	Val	Glu	Thr	Val	Gly	Gly	Gln	Met	Gln	Leu	Arg	Asp	Glu
				200					205					210
Arg	Val	Val	Ala	Ala	Leu	Phe	Ile	Leu	Leu	Gln	Phe	Phe	Phe	Gln
				215					220					225
Lys	Gln	Pro	Ser	Leu	Leu	Pro	Glu	Gly	Leu	Trp	Leu	Leu	Asn	Asn
				230					235					240
Leu	Thr	Ala	Asn	Ser	Pro	Ser	Phe	Cys	Thr	Ser	Leu	Leu	Ser	Leu
				245					250					255
Asp	Leu	Ile	Glu	Pro	Leu	Leu	Gln	Leu	Leu	Pro	Val	Ser	Asn	Val
				260					265					270
Val	Ser	Val	Met	Val	Leu	Thr	Val	Leu	Cys	Asn	Val	Ala	Glu	Lys
				275					280					285
Gly	Pro	Ala	Tyr	Cys	Gln	Arg	Leu	Trp	Pro	Gly	Pro	Leu	Leu	Pro
				290					295					300
Ala	Leu	Leu	His	Thr	Leu	Ala	Phe	Ser	Asp	Thr	Glu	Val	Val	Gly
				305					310					315
Gln	Ser	Leu	Glu	Leu	Leu	His	Leu	Leu	Phe	Leu	Tyr	Gln	Pro	Glu
				320					325					330
Ala	Val	Gln	Val	Phe	Leu	Gln	Gln	Ser	Gly	Leu	Gln	Ala	Trp	Lys
				335					340					345
Arg	His	Gln	Glu	Glu	Ala	Gln	Leu	Gln	Asp	Arg	Val	Tyr	Ala	Leu
				350					355					360
Gln	Gln	Thr	Ala	Leu	Gln	Gly								
				365										

<210> 36

<211> 1113

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1243349CD1

<400> 36

Met	Ile	Ala	Val	Ser	Phe	Lys	Cys	Arg	Cys	Gln	Ile	Leu	Arg	Arg
1				5					10					15
Leu	Thr	Lys	Asp	Glu	Ser	Pro	Tyr	Thr	Lys	Ser	Ala	Ser	Gln	Thr
				20					25					30
Lys	Pro	Pro	Asp	Gly	Ala	Leu	Ala	Val	Arg	Arg	Gln	Ser	Ile	Pro
				35					40					45
Glu	Glu	Phe	Lys	Gly	Ser	Thr	Val	Val	Glu	Leu	Met	Lys	Lys	Glu
				50					55					60
Gly	Thr	Thr	Leu	Gly	Leu	Thr	Val	Ser	Gly	Gly	Ile	Asp	Lys	Asp
				65					70					75
Gly	Lys	Pro	Arg	Val	Ser	Asn	Leu	Arg	Gln	Gly	Gly	Ile	Ala	Ala
				80					85					90
Arg	Ser	Asp	Gln	Leu	Asp	Val	Gly	Asp	Tyr	Ile	Lys	Ala	Val	Asn
				95					100					105
Gly	Ile	Asn	Leu	Ala	Lys	Phe	Arg	His	Asp	Glu	Ile	Ile	Ser	Leu
				110					115					120
Leu	Lys	Asn	Val	Gly	Glu	Arg	Val	Val	Leu	Glu	Val	Glu	Tyr	Glu
				125					130					135
Leu	Pro	Pro	Val	Ser	Val	Gln	Gly	Ser	Ser	Val	Ile	Phe	Arg	Thr

				140					145					150
Val	Glu	Val	Thr	Leu	His	Lys	Glu	Gly	Asn	Thr	Phe	Gly	Phe	Val
				155					160					165
Ile	Arg	Gly	Gly	Ala	His	Asp	Asp	Arg	Asn	Lys	Ser	Arg	Pro	Val
				170					175					180
Val	Ile	Thr	Cys	Val	Arg	Pro	Gly	Gly	Pro	Ala	Asp	Arg	Glu	Gly
				185					190					195
Thr	Ile	Lys	Pro	Gly	Asp	Arg	Leu	Leu	Ser	Val	Asp	Gly	Ile	Arg
				200					205					210
Leu	Leu	Gly	Thr	Thr	His	Ala	Glu	Ala	Met	Ser	Ile	Leu	Lys	Gln
				215					220					225
Cys	Gly	Gln	Glu	Ala	Ala	Leu	Leu	Ile	Glu	Tyr	Asp	Val	Ser	Val
				230					235					240
Met	Asp	Ser	Val	Ala	Thr	Ala	Ser	Gly	Pro	Leu	Leu	Val	Glu	Val
				245					250					255
Ala	Lys	Thr	Pro	Gly	Ala	Ser	Leu	Gly	Val	Ala	Leu	Thr	Thr	Ser
				260					265					270
Met	Cys	Cys	Asn	Lys	Gln	Val	Ile	Val	Ile	Asp	Lys	Ile	Lys	Ser
				275					280					285
Ala	Ser	Ile	Ala	Asp	Arg	Cys	Gly	Ala	Leu	His	Val	Gly	Asp	His
				290					295					300
Ile	Leu	Ser	Ile	Asp	Gly	Thr	Ser	Met	Glu	Tyr	Cys	Thr	Leu	Ala
				305					310					315
Glu	Ala	Thr	Gln	Phe	Leu	Ala	Asn	Thr	Thr	Asp	Gln	Val	Lys	Leu
				320					325					330
Glu	Ile	Leu	Pro	His	His	Gln	Thr	Arg	Leu	Ala	Leu	Lys	Gly	Pro
				335					340					345
Asp	His	Val	Lys	Ile	Gln	Arg	Ser	Asp	Arg	Gln	Leu	Thr	Trp	Asp
				350					355					360
Ser	Trp	Ala	Ser	Asn	His	Ser	Ser	Leu	His	Thr	Asn	His	His	Tyr
				365					370					375
Asn	Thr	Tyr	His	Pro	Asp	His	Cys	Arg	Val	Pro	Ala	Leu	Thr	Phe
				380					385					390
Pro	Lys	Ala	Pro	Pro	Pro	Asn	Ser	Pro	Pro	Ala	Leu	Val	Ser	Ser
				395					400					405
Ser	Phe	Ser	Pro	Thr	Ser	Met	Ser	Ala	Tyr	Ser	Leu	Ser	Ser	Leu
				410					415					420
Asn	Met	Gly	Thr	Leu	Pro	Arg	Ser	Leu	Tyr	Ser	Thr	Ser	Pro	Arg
				425					430					435
Gly	Thr	Met	Met	Arg	Arg	Arg	Leu	Lys	Lys	Lys	Asp	Phe	Lys	Ser
				440					445					450
Ser	Leu	Ser	Leu	Ala	Ser	Ser	Thr	Val	Gly	Leu	Ala	Gly	Gln	Val
				455					460					465
Val	His	Thr	Glu	Thr	Thr	Glu	Val	Val	Leu	Thr	Ala	Asp	Pro	Val
				470					475					480
Thr	Gly	Phe	Gly	Ile	Gln	Leu	Gln	Gly	Ser	Val	Phe	Ala	Thr	Glu
				485					490					495
Thr	Leu	Ser	Ser	Pro	Pro	Leu	Ile	Ser	Tyr	Ile	Glu	Ala	Asp	Ser
				500					505					510
Pro	Ala	Glu	Arg	Cys	Gly	Val	Leu	Gln	Ile	Gly	Asp	Arg	Val	Met
				515					520					525
Ala	Ile	Asn	Gly	Ile	Pro	Thr	Glu	Asp	Ser	Thr	Phe	Glu	Glu	Ala
				530					535					540
Ser	Gln	Leu	Leu	Arg	Asp	Ser	Ser	Ile	Thr	Ser	Lys	Val	Thr	Leu
				545					550					555
Glu	Ile	Glu	Phe	Asp	Val	Ala	Glu	Ser	Val	Ile	Pro	Ser	Ser	Gly
				560					565					570
Thr	Phe	His	Val	Lys	Leu	Pro	Lys	Lys	His	Asn	Val	Glu	Leu	Gly
				575					580					585
Ile	Thr	Ile	Ser	Ser	Pro	Ser	Ser	Arg	Lys	Pro	Gly	Asp	Pro	Leu
				590					595					600
Val	Ile	Ser	Asp	Ile	Lys	Lys	Gly	Ser	Val	Ala	His	Arg	Thr	Gly
				605					610					615
Thr	Leu	Glu	Leu	Gly	Asp	Lys	Leu	Leu	Ala	Ile	Asp	Asn	Ile	Arg
				620					625					630
Leu	Asp	Asn	Cys	Ser	Met	Glu	Asp	Ala	Val	Gln	Ile	Leu	Gln	Gln
				635					640					645

Cys	Glu	Asp	Leu	Val	Lys	Leu	Lys	Ile	Arg	Lys	Asp	Glu	Asp	Asn
				650					655					660
Ser	Asp	Glu	Gln	Glu	Ser	Ser	Gly	Ala	Ile	Ile	Tyr	Thr	Val	Glu
				665					670					675
Leu	Lys	Arg	Tyr	Gly	Gly	Pro	Leu	Gly	Ile	Thr	Ile	Ser	Gly	Thr
				680					685					690
Glu	Glu	Pro	Phe	Asp	Pro	Ile	Ile	Ile	Ser	Ser	Leu	Thr	Lys	Gly
				695					700					705
Gly	Leu	Ala	Glu	Arg	Thr	Gly	Ala	Ile	His	Ile	Gly	Asp	Arg	Ile
				710					715					720
Leu	Ala	Ile	Asn	Ser	Ser	Ser	Leu	Lys	Gly	Lys	Pro	Leu	Ser	Glu
				725					730					735
Ala	Ile	His	Leu	Leu	Gln	Met	Ala	Gly	Glu	Thr	Val	Thr	Leu	Lys
				740					745					750
Ile	Lys	Lys	Gln	Thr	Asp	Ala	Gln	Ser	Ala	Ser	Ser	Pro	Lys	Lys
				755					760					765
Phe	Pro	Ile	Ser	Ser	His	Leu	Ser	Asp	Leu	Gly	Asp	Val	Glu	Glu
				770					775					780
Asp	Ser	Ser	Pro	Ala	Gln	Lys	Pro	Gly	Lys	Leu	Ser	Asp	Met	Tyr
				785					790					795
Pro	Ser	Thr	Val	Pro	Ser	Val	Asp	Ser	Ala	Val	Asp	Ser	Trp	Asp
				800					805					810
Gly	Ser	Ala	Ile	Asp	Thr	Ser	Tyr	Gly	Thr	Glu	Gly	Thr	Ser	Phe
				815					820					825
Gln	Ala	Ser	Gly	Tyr	Asn	Phe	Asn	Thr	Tyr	Asp	Trp	Arg	Ser	Pro
				830					835					840
Lys	Gln	Arg	Gly	Ser	Leu	Ser	Pro	Val	Thr	Lys	Pro	Arg	Ser	Gln
				845					850					855
Thr	Tyr	Pro	Asp	Val	Gly	Leu	Ser	Tyr	Glu	Asp	Trp	Asp	Arg	Ser
				860					865					870
Thr	Ala	Ser	Gly	Phe	Ala	Gly	Ala	Ala	Asp	Ser	Ala	Glu	Thr	Glu
				875					880					885
Gln	Glu	Glu	Asn	Phe	Trp	Ser	Gln	Ala	Leu	Glu	Asp	Leu	Glu	Thr
				890					895					900
Cys	Gly	Gln	Ser	Gly	Ile	Leu	Arg	Glu	Leu	Glu	Ala	Thr	Ile	Met
				905					910					915
Ser	Gly	Ser	Thr	Met	Ser	Leu	Asn	His	Glu	Ala	Pro	Thr	Pro	Arg
				920					925					930
Ser	Gln	Leu	Gly	Arg	Gln	Ala	Ser	Phe	Gln	Glu	Arg	Ser	Ser	Ser
				935					940					945
Arg	Pro	His	Tyr	Ser	Gln	Thr	Thr	Arg	Ser	Asn	Thr	Leu	Pro	Ser
				950					955					960
Asp	Val	Gly	Arg	Lys	Ser	Val	Thr	Leu	Arg	Lys	Met	Lys	Gln	Glu
				965					970					975
Ile	Lys	Glu	Ile	Met	Ser	Pro	Thr	Pro	Val	Glu	Leu	His	Lys	Val
				980					985					990
Thr	Leu	Tyr	Lys	Asp	Ser	Asp	Met	Glu	Asp	Phe	Gly	Phe	Ser	Val
				995					1000					1005
Ala	Asp	Gly	Leu	Glu	Glu	Lys	Gly	Val	Tyr	Val	Lys	Asn	Ile	Arg
				1010					1015					1020
Pro	Ala	Gly	Pro	Gly	Asp	Leu	Gly	Gly	Leu	Lys	Pro	Tyr	Asp	Arg
				1025					1030					1035
Leu	Leu	Gln	Val	Asn	His	Val	Arg	Thr	Arg	Asp	Phe	Asp	Cys	Cys
				1040					1045					1050
Leu	Val	Val	Pro	Leu	Ile	Ala	Glu	Ser	Gly	Asn	Lys	Leu	Asp	Leu
				1055					1060					1065
Val	Ile	Ser	Arg	Asn	Pro	Leu	Ala	Ser	Gln	Lys	Ser	Ile	Asp	Gln
				1070					1075					1080
Gln	Ser	Leu	Pro	Gly	Asp	Trp	Ser	Glu	Gln	Asn	Ser	Ala	Phe	Phe
				1085					1090					1095
Gln	Gln	Pro	Ser	His	Gly	Gly	Asn	Leu	Glu	Thr	Arg	Glu	Pro	Thr
				1100					1105					1110

Asn Thr Leu

<210> 37
 <211> 511
 <212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1338201CD1

<400> 37

Met	Ser	Arg	Gly	Pro	Glu	Glu	Val	Asn	Arg	Leu	Thr	Glu	Ser	Thr	1	5	10	15
Tyr	Arg	Asn	Val	Met	Glu	Gln	Phe	Asn	Pro	Gly	Leu	Arg	Asn	Leu	20	25	30	35
Ile	Asn	Leu	Gly	Lys	Asn	Tyr	Glu	Lys	Ala	Val	Asn	Ala	Met	Ile	40	45	50	55
Leu	Ala	Gly	Lys	Ala	Tyr	Tyr	Asp	Gly	Val	Ala	Lys	Ile	Gly	Glu	60	65	70	75
Ile	Ala	Thr	Gly	Ser	Pro	Val	Ser	Thr	Glu	Leu	Gly	His	Val	Leu	80	85	90	95
Ile	Glu	Ile	Ser	Ser	Thr	His	Lys	Lys	Leu	Asn	Glu	Ser	Leu	Asp	100	105	110	115
Glu	Asn	Phe	Lys	Lys	Phe	His	Lys	Glu	Ile	Ile	His	Glu	Leu	Glu	120	125	130	135
Lys	Lys	Ile	Glu	Leu	Asp	Val	Lys	Tyr	Met	Asn	Ala	Thr	Leu	Lys	140	145	150	155
Arg	Tyr	Gln	Thr	Glu	His	Lys	Asn	Lys	Leu	Glu	Ser	Leu	Glu	Lys	160	165	170	175
Ser	Gln	Ala	Glu	Leu	Lys	Lys	Ile	Arg	Arg	Lys	Ser	Gln	Gly	Ser	180	185	190	195
Arg	Asn	Ala	Leu	Lys	Tyr	Glu	His	Lys	Glu	Ile	Glu	Tyr	Val	Glu	200	205	210	215
Thr	Val	Thr	Ser	Arg	Gln	Ser	Glu	Ile	Gln	Lys	Phe	Ile	Ala	Asp	220	225	230	235
Gly	Cys	Lys	Glu	Ala	Leu	Leu	Glu	Glu	Lys	Arg	Arg	Phe	Cys	Phe	240	245	250	255
Leu	Val	Asp	Lys	His	Cys	Gly	Phe	Ala	Asn	His	Ile	His	Tyr	Tyr	260	265	270	275
His	Leu	Gln	Ser	Ala	Glu	Leu	Leu	Asn	Ser	Lys	Leu	Pro	Arg	Trp	280	285	290	295
Gln	Glu	Thr	Cys	Val	Asp	Ala	Ile	Lys	Val	Pro	Glu	Lys	Ile	Met	300	305	310	315
Asn	Met	Ile	Glu	Glu	Ile	Lys	Thr	Pro	Ala	Ser	Thr	Pro	Val	Ser	320	325	330	335
Gly	Thr	Pro	Gln	Ala	Ser	Pro	Met	Ile	Glu	Arg	Ser	Asn	Val	Val	340	345	350	355
Arg	Lys	Asp	Tyr	Asp	Thr	Leu	Ser	Lys	Cys	Ser	Pro	Lys	Met	Pro	360	365	370	375
Pro	Ala	Pro	Ser	Gly	Arg	Ala	Tyr	Thr	Ser	Pro	Leu	Ile	Asp	Met	380	385	390	395
Phe	Asn	Asn	Pro	Ala	Thr	Ala	Ala	Pro	Asn	Ser	Gln	Arg	Val	Asn	400	405	410	415
Asn	Ser	Thr	Gly	Thr	Ser	Glu	Asp	Pro	Ser	Leu	Gln	Arg	Ser	Val	420	425	430	435
Ser	Val	Ala	Thr	Gly	Leu	Asn	Met	Met	Lys	Lys	Gln	Lys	Val	Lys	440	445	450	
Thr	Ile	Phe	Pro	His	Thr	Ala	Gly	Ser	Asn	Lys	Thr	Leu	Leu	Ser				
Phe	Ala	Gln	Gly	Asp	Val	Ile	Thr	Leu	Leu	Ile	Pro	Glu	Glu	Lys				
Asp	Gly	Trp	Leu	Tyr	Gly	Glu	His	Asp	Val	Ser	Lys	Ala	Arg	Gly				
Trp	Phe	Pro	Ser	Ser	Tyr	Thr	Lys	Leu	Leu	Glu	Glu	Asn	Glu	Thr				
Glu	Ala	Val	Thr	Val	Pro	Thr	Pro	Ser	Pro	Thr	Pro	Val	Arg	Ser				
Ile	Ser	Thr	Val	Asn	Leu	Ser	Glu	Asn	Ser	Ser	Val	Val	Ile	Pro				
Pro	Pro	Asp	Tyr	Leu	Glu	Cys	Leu	Ser	Met	Gly	Ala	Ala	Ala	Asp				

Arg	Arg	Ala	Asp	Ser	Ala	Arg	Thr	Thr	Ser	Thr	Phe	Lys	Ala	Pro
				455					460					465
Ala	Ser	Lys	Pro	Glu	Thr	Ala	Ala	Pro	Asn	Asp	Ala	Asn	Gly	Thr
				470					475					480
Ala	Lys	Pro	Pro	Phe	Leu	Ser	Gly	Glu	Asn	Pro	Phe	Ala	Thr	Val
				485					490					495
Lys	Leu	Arg	Pro	Thr	Val	Thr	Asn	Asp	Arg	Ser	Ala	Pro	Ile	Ile
				500					505					510

Arg

<210> 38

<211> 1177

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1405141CD1

<400> 38

Met	Thr	Thr	Ile	Leu	Lys	Pro	Ser	Ala	Asp	Phe	Leu	Thr	Ser	Asn
1				5					10					15
Lys	Leu	Leu	Lys	Tyr	Ser	Trp	Phe	Phe	Phe	Asp	Val	Leu	Ile	Lys
				20					25					30
Ser	Met	Ala	Gln	His	Leu	Ile	Glu	Asn	Ser	Lys	Val	Lys	Leu	Leu
				35					40					45
Arg	Asn	Gln	Arg	Phe	Pro	Ala	Ser	Tyr	His	His	Ala	Val	Glu	Thr
				50					55					60
Val	Val	Asn	Met	Leu	Met	Pro	His	Ile	Thr	Gln	Lys	Phe	Arg	Asp
				65					70					75
Asn	Pro	Glu	Ala	Ser	Lys	Asn	Ala	Asn	His	Ser	Leu	Ala	Val	Phe
				80					85					90
Ile	Lys	Arg	Cys	Phe	Thr	Phe	Met	Asp	Arg	Gly	Phe	Val	Phe	Lys
				95					100					105
Gln	Ile	Asn	Asn	Tyr	Ile	Ser	Cys	Phe	Ala	Pro	Gly	Asp	Pro	Lys
				110					115					120
Thr	Leu	Phe	Glu	Tyr	Lys	Phe	Glu	Phe	Leu	Arg	Val	Val	Cys	Asn
				125					130					135
His	Glu	His	Tyr	Ile	Pro	Leu	Asn	Leu	Pro	Met	Pro	Phe	Gly	Lys
				140					145					150
Gly	Arg	Ile	Gln	Arg	Tyr	Gln	Asp	Leu	Gln	Leu	Asp	Tyr	Ser	Leu
				155					160					165
Thr	Asp	Glu	Phe	Cys	Arg	Asn	His	Phe	Leu	Val	Gly	Leu	Leu	Leu
				170					175					180
Arg	Glu	Val	Gly	Thr	Ala	Leu	Gln	Glu	Phe	Arg	Glu	Val	Arg	Leu
				185					190					195
Ile	Ala	Ile	Ser	Val	Leu	Lys	Asn	Leu	Leu	Ile	Lys	His	Ser	Phe
				200					205					210
Asp	Asp	Arg	Tyr	Ala	Ser	Arg	Ser	His	Gln	Ala	Arg	Ile	Ala	Thr
				215					220					225
Leu	Tyr	Leu	Pro	Leu	Phe	Gly	Leu	Leu	Ile	Glu	Asn	Val	Gln	Arg
				230					235					240
Ile	Asn	Val	Arg	Asp	Val	Ser	Pro	Phe	Pro	Val	Asn	Ala	Gly	Met
				245					250					255
Thr	Val	Lys	Asp	Glu	Ser	Leu	Ala	Leu	Pro	Ala	Val	Asn	Pro	Leu
				260					265					270
Val	Thr	Pro	Gln	Lys	Gly	Ser	Thr	Leu	Asp	Asn	Ser	Leu	His	Lys
				275					280					285
Asp	Leu	Leu	Gly	Ala	Ile	Ser	Gly	Ile	Ala	Ser	Pro	Tyr	Thr	Thr
				290					295					300
Ser	Thr	Pro	Asn	Ile	Asn	Ser	Val	Arg	Asn	Ala	Asp	Ser	Arg	Gly
				305					310					315
Ser	Leu	Ile	Ser	Thr	Asp	Ser	Gly	Asn	Ser	Leu	Pro	Glu	Arg	Asn
				320					325					330
Ser	Glu	Lys	Ser	Asn	Ser	Leu	Asp	Lys	His	Gln	Gln	Ser	Ser	Thr
				335					340					345
Leu	Gly	Asn	Ser	Val	Val	Arg	Cys	Asp	Lys	Leu	Asp	Gln	Ser	Glu

	350		355		360
Ile Lys Ser Leu	Leu Met Cys Phe Leu Tyr	Ile Leu Lys Ser	Met		
	365		370		375
Ser Asp Asp Ala	Leu Phe Thr Tyr Trp Asn	Lys Ala Ser Thr	Ser		
	380		385		390
Glu Leu Met Asp	Phe Phe Thr Ile Ser Glu	Val Cys Leu His	Gln		
	395		400		405
Phe Gln Tyr Met	Gly Lys Arg Tyr Ile Ala	Ser Val Arg Lys	Ile		
	410		415		420
Ser Ser Val Leu	Gly Ile Ser Val Asp Asn	Gly Tyr Gly His	Ser		
	425		430		435
Asp Ala Asp Val	Leu His Gln Ser Leu Leu	Glu Ala Asn Ile	Ala		
	440		445		450
Thr Glu Val Cys	Leu Thr Ala Leu Asp Thr	Leu Ser Leu Phe	Thr		
	455		460		465
Leu Ala Phe Lys	Asn Gln Leu Leu Ala Asp	His Gly His Asn	Pro		
	470		475		480
Leu Met Lys Lys	Val Phe Asp Val Tyr Leu	Cys Phe Leu Gln	Lys		
	485		490		495
His Gln Ser Glu	Thr Ala Leu Lys Asn Val	Phe Thr Ala Leu	Arg		
	500		505		510
Ser Leu Ile Tyr	Lys Phe Pro Ser Thr Phe	Tyr Glu Gly Arg	Ala		
	515		520		525
Asp Met Cys Ala	Ala Leu Cys Tyr Glu Ile	Leu Lys Cys Cys	Asn		
	530		535		540
Ser Lys Leu Ser	Ser Ile Arg Thr Glu Ala	Ser Gln Leu Leu	Tyr		
	545		550		555
Phe Leu Met Arg	Asn Asn Phe Asp Tyr Thr	Gly Lys Lys Ser	Phe		
	560		565		570
Val Arg Thr His	Leu Gln Val Ile Ile Ser	Val Ser Gln Leu	Ile		
	575		580		585
Ala Asp Val Val	Gly Ile Gly Gly Thr Arg	Phe Gln Gln Ser	Leu		
	590		595		600
Ser Ile Ile Asn	Asn Cys Ala Asn Ser Asp	Arg Leu Ile Lys	His		
	605		610		615
Thr Ser Phe Ser	Ser Asp Val Lys Asp Leu	Thr Lys Arg Ile	Arg		
	620		625		630
Thr Val Leu Met	Ala Thr Ala Gln Met Lys	Glu His Glu Asn	Asp		
	635		640		645
Pro Glu Met Leu	Val Asp Leu Gln Tyr Ser	Leu Ala Lys Ser	Tyr		
	650		655		660
Ala Ser Thr Pro	Glu Leu Arg Lys Thr Trp	Leu Asp Ser Met	Ala		
	665		670		675
Arg Ile His Val	Lys Asn Gly Asp Leu Ser	Glu Ala Ala Met	Cys		
	680		685		690
Tyr Val His Val	Thr Ala Leu Val Ala Glu	Tyr Leu Thr Arg	Lys		
	695		700		705
Gly Val Phe Arg	Gln Gly Cys Thr Ala Phe	Arg Val Ile Thr	Pro		
	710		715		720
Asn Ile Asp Glu	Glu Ala Ser Met Met Glu	Asp Val Gly Met	Gln		
	725		730		735
Asp Val His Phe	Asn Glu Asp Val Leu Met	Glu Leu Leu Glu	Gln		
	740		745		750
Cys Ala Asp Gly	Leu Trp Lys Ala Glu Arg	Tyr Glu Leu Ile	Ala		
	755		760		765
Asp Ile Tyr Lys	Leu Ile Ile Pro Ile Tyr	Glu Lys Arg Arg	Asp		
	770		775		780
Phe Glu Arg Leu	Ala His Leu Tyr Asp Thr	Leu His Arg Ala	Tyr		
	785		790		795
Ser Lys Val Thr	Glu Val Met His Ser Gly	Arg Ser Val Leu	Gly		
	800		805		810
Thr Tyr Phe Arg	Val Ala Phe Phe Gly Gln	Gly Phe Phe Glu	Asp		
	815		820		825
Glu Asp Gly Lys	Glu Tyr Ile Tyr Lys Glu	Pro Lys Leu Thr	Pro		
	830		835		840
Leu Ser Glu Ile	Ser Gln Arg Leu Leu Lys	Leu Tyr Ser Asp	Lys		
	845		850		855

Phe Gly Ser Glu Asn Val Lys Met Ile Gln Asp Ser Gly Lys Val
 860 865 870
 Asn Pro Lys Asp Leu Asp Ser Lys Tyr Ala Tyr Ile Gln Val Thr
 875 880 885
 His Val Ile Pro Phe Asp Glu Lys Glu Leu Gln Glu Arg Lys
 890 895 900
 Thr Glu Phe Glu Arg Ser His Asn Ile Arg Arg Phe Met Phe Glu
 905 910 915
 Met Pro Phe Thr Gln Thr Gly Lys Arg Gln Gly Gly Val Glu Glu
 920 925 930
 Gln Cys Lys Arg Arg Thr Ile Leu Thr Ala Ile His Cys Phe Pro
 935 940 945
 Tyr Val Lys Lys Arg Ile Pro Val Met Tyr Gln His His Thr Asp
 950 955 960
 Leu Asn Pro Ile Glu Val Ala Ile Asp Glu Met Ser Lys Lys Val
 965 970 975
 Ala Glu Leu Arg Gln Leu Cys Ser Ser Ala Glu Val Asp Met Ile
 980 985 990
 Lys Leu Gln Leu Lys Leu Gln Gly Ser Val Ser Val Gln Val Asn
 995 1000 1005
 Ala Gly Pro Leu Ala Tyr Ala Arg Ala Phe Leu Asp Asp Thr Asn
 1010 1015 1020
 Thr Lys Arg Tyr Pro Asp Asn Lys Val Lys Leu Leu Lys Glu Val
 1025 1030 1035
 Phe Arg Gln Phe Val Glu Ala Cys Gly Gln Ala Leu Ala Val Asn
 1040 1045 1050
 Glu Arg Leu Ile Lys Glu Asp Gln Leu Glu Tyr Gln Glu Glu Met
 1055 1060 1065
 Lys Ala Asn Tyr Arg Glu Met Ala Lys Glu Leu Ser Glu Ile Met
 1070 1075 1080
 His Glu Gln Ile Cys Pro Leu Glu Asp Glu Asp Glu Arg Leu Thr
 1085 1090 1095
 Glu Phe Pro Ser His Leu Gln Arg His Gln Trp Asp Ser Asn Lys
 1100 1105 1110
 His Asn Gly Ser Arg Asp Asp Gln Leu Val Phe Gly Arg Val Ile
 1115 1120 1125
 Thr Ser His Gly Pro Cys Val Gly Thr Cys Phe Val Ile Cys Lys
 1130 1135 1140
 Leu Arg Met Leu Ser Lys Ala Asn His Trp Gly Asp Arg Ala Gln
 1145 1150 1155
 Gly Gly Pro Arg Gly Arg Gly Glu Lys Gly Asn Lys Glu Gln Arg
 1160 1165 1170
 Tyr Phe Leu Thr Asp Phe Leu
 1175

<210> 39

<211> 665

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1686305CD1

<400> 39

Met Thr Ser Ala Asn Lys Ala Ile Glu Leu Gln Leu Gln Val Lys
 1 5 10 15
 Gln Asn Ala Glu Glu Leu Gln Asp Phe Met Arg Asp Leu Glu Asn
 20 25 30
 Trp Glu Lys Asp Ile Lys Gln Lys Asp Met Glu Leu Arg Arg Gln
 35 40 45
 Asn Gly Val Pro Glu Glu Asn Leu Pro Pro Ile Arg Asn Gly Asn
 50 55 60
 Phe Arg Lys Lys Lys Lys Gly Lys Ala Lys Glu Ser Ser Lys Lys
 65 70 75
 Thr Arg Glu Glu Asn Thr Lys Asn Arg Ile Lys Ser Tyr Asp Tyr
 80 85 90
 Glu Ala Trp Ala Lys Leu Asp Val Asp Arg Ile Leu Asp Glu Leu

	95		100		105
Asp Lys Asp Asp	Ser Thr His Glu Ser	Leu Ser Gln Glu Ser	Glu		
	110		115		120
Ser Glu Glu Asp	Gly Ile His Val Asp	Ser Gln Lys Ala Leu	Val		
	125		130		135
Leu Lys Glu Lys	Gly Asn Lys Tyr Phe	Lys Gln Gly Lys Tyr	Asp		
	140		145		150
Glu Ala Ile Asp	Cys Tyr Thr Lys Gly	Met Asp Ala Asp Pro	Tyr		
	155		160		165
Asn Pro Val Leu	Pro Thr Asn Arg Ala	Ser Ala Tyr Phe Arg	Leu		
	170		175		180
Lys Lys Phe Ala	Val Ala Glu Ser Asp	Cys Asn Leu Ala Val	Ala		
	185		190		195
Leu Asn Arg Ser	Tyr Thr Lys Ala Tyr	Ser Arg Arg Gly Ala	Ala		
	200		205		210
Arg Phe Ala Leu	Gln Lys Leu Glu Glu	Ala Lys Lys Asp Tyr	Glu		
	215		220		225
Arg Val Leu Glu	Leu Glu Pro Asn Asn	Phe Glu Ala Thr Asn	Glu		
	230		235		240
Leu Arg Lys Ile	Ser Gln Ala Leu Ala	Ser Lys Glu Asn Ser	Tyr		
	245		250		255
Pro Lys Glu Ala	Asp Ile Val Ile Lys	Ser Thr Glu Gly Glu	Arg		
	260		265		270
Lys Gln Ile Glu	Ala Gln Gln Asn Lys	Gln Gln Ala Ile Ser	Glu		
	275		280		285
Lys Asp Arg Gly	Asn Gly Phe Phe Lys	Glu Gly Lys Tyr Glu	Arg		
	290		295		300
Ala Ile Glu Cys	Tyr Thr Arg Gly Ile	Ala Ala Asp Gly Ala	Asn		
	305		310		315
Ala Leu Leu Pro	Ala Asn Arg Ala Met	Ala Tyr Leu Lys Ile	Gln		
	320		325		330
Lys Tyr Glu Glu	Ala Glu Lys Asp Cys	Thr Gln Ala Ile Leu	Leu		
	335		340		345
Asp Gly Ser Tyr	Ser Lys Ala Phe Ala	Arg Arg Gly Thr Ala	Arg		
	350		355		360
Thr Phe Leu Gly	Lys Leu Asn Glu Ala	Lys Gln Asp Phe Glu	Thr		
	365		370		375
Val Leu Leu Leu	Glu Pro Gly Asn Lys	Gln Ala Val Thr Glu	Leu		
	380		385		390
Ser Lys Ile Lys	Lys Glu Leu Ile Glu	Lys Gly His Trp Asp	Asp		
	395		400		405
Val Phe Leu Asp	Ser Thr Gln Arg Gln	Asn Val Val Lys Pro	Ile		
	410		415		420
Asp Asn Pro Pro	His Pro Gly Ser Thr	Lys Pro Leu Lys Lys	Val		
	425		430		435
Ile Ile Glu Glu	Thr Gly Asn Leu Ile	Gln Thr Ile Asp Val	Pro		
	440		445		450
Asp Ser Thr Thr	Ala Ala Ala Pro Glu	Asn Asn Pro Ile Asn	Leu		
	455		460		465
Ala Asn Val Ile	Ala Ala Thr Gly Thr	Thr Ser Lys Lys Asn	Ser		
	470		475		480
Ser Gln Asp Asp	Leu Phe Pro Thr Ser	Asp Thr Pro Arg Ala	Lys		
	485		490		495
Val Leu Lys Ile	Glu Glu Val Ser Asp	Thr Ser Ser Leu Gln	Pro		
	500		505		510
Gln Ala Ser Leu	Lys Gln Asp Val Cys	Gln Ser Tyr Ser Glu	Lys		
	515		520		525
Met Pro Ile Glu	Ile Glu Gln Lys Pro	Ala Gln Phe Ala Thr	Thr		
	530		535		540
Val Leu Pro Pro	Ile Pro Ala Asn Ser	Phe Gln Leu Glu Ser	Asp		
	545		550		555
Phe Arg Gln Leu	Lys Ser Ser Pro Asp	Met Leu Tyr Gln Tyr	Leu		
	560		565		570
Lys Gln Ile Glu	Pro Ser Leu Tyr Pro	Lys Leu Phe Gln Lys	Asn		
	575		580		585
Leu Asp Pro Asp	Val Phe Asn Gln Ile	Val Lys Ile Leu His	Asp		
	590		595		600

Phe Tyr Ile Glu Lys Glu Lys Pro Leu Leu Ile Phe Glu Ile Leu
 605 610 615
 Gln Arg Leu Ser Glu Leu Lys Arg Phe Asp Met Ala Val Met Phe
 620 625 630
 Met Ser Glu Thr Glu Lys Lys Ile Ala Arg Ala Leu Phe Asn His
 635 640 645
 Ile Asp Lys Ser Gly Leu Lys Asp Ser Ser Val Glu Glu Leu Lys
 650 655 660
 Lys Arg Tyr Gly Gly
 665

<210> 40

<211> 125

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1688972CD1

<400> 40

Met Leu Asp Leu Gln Lys Gln Leu Gly Arg Phe Pro Gly Thr Phe
 1 5 10 15
 Val Gly Thr Thr Glu Pro Ala Ser Pro Pro Leu Ser Ser Thr Ser
 20 25 30
 Pro Thr Thr Ala Ala Ala Thr Met Pro Val Val Pro Ser Val Ala
 35 40 45
 Ser Leu Ala Pro Pro Gly Glu Ala Ser Leu Cys Leu Glu Glu Val
 50 55 60
 Ala Pro Pro Ala Ser Gly Thr Arg Lys Ala Arg Val Leu Tyr Asp
 65 70 75
 Tyr Glu Ala Ala Asp Ser Ser Glu Leu Ala Leu Leu Ala Asp Glu
 80 85 90
 Leu Ile Thr Val Tyr Ser Leu Pro Gly Met Asp Pro Asp Trp Leu
 95 100 105
 Ile Gly Glu Arg Gly Asn Lys Lys Gly Lys Val Pro Val Thr Tyr
 110 115 120
 Leu Glu Leu Leu Ser
 125

<210> 41

<211> 366

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1812494CD1

<400> 41

Met Cys Tyr Phe Tyr Leu Gly Asp Lys Ile Lys Thr Ile Ser Phe
 1 5 10 15
 Gln Ala Phe Ile Leu Met His Leu Leu Leu Pro Ser Glu Tyr Ser
 20 25 30
 Leu Asp Gly Phe His Met Ser Gly Phe Ser Leu Gly Ser Gly Ser
 35 40 45
 Glu Gly Glu Asp Gly Phe Gln Val Glu Leu Glu Leu Val Glu Leu
 50 55 60
 Thr Val Gly Thr Leu Asp Leu Cys Glu Ser Glu Val Leu Pro Lys
 65 70 75
 Arg Arg Arg Arg Lys Arg Asn Lys Lys Glu Lys Ser Arg Asp Gln
 80 85 90
 Glu Ala Gly Ala His Arg Thr Leu Leu Gln Gln Thr Gln Glu Glu
 95 100 105
 Glu Pro Ser Thr Gln Ser Ser Gln Ala Val Ala Ala Pro Leu Gly
 110 115 120
 Pro Leu Leu Asp Glu Ala Lys Ala Pro Gly Gln Pro Glu Leu Trp
 125 130 135
 Asn Ala Leu Leu Ala Ala Cys Arg Ala Gly Asp Val Gly Val Leu

Lys	Leu	Gln	Leu	Ala	Pro	Ser	Pro	Ala	Asp	Pro	Arg	Val	Leu	Ser
Leu	Leu	Ser	Ala	Pro	Leu	Gly	Ser	Gly	Gly	Phe	Thr	Leu	Leu	His
Ala	Ala	Ala	Ala	Ala	Gly	Arg	Gly	Ser	Val	Val	Arg	Leu	Leu	Leu
Glu	Ala	Gly	Ala	Asp	Pro	Thr	Val	Gln	Asp	Ser	Arg	Ala	Arg	Pro
Pro	Tyr	Thr	Val	Ala	Ala	Asp	Lys	Ser	Thr	Arg	Asn	Glu	Phe	Arg
Arg	Phe	Met	Glu	Lys	Asn	Pro	Asp	Ala	Tyr	Asp	Tyr	Asn	Lys	Ala
Gln	Val	Pro	Gly	Pro	Leu	Thr	Pro	Glu	Met	Glu	Ala	Arg	Gln	Ala
Thr	Arg	Lys	Arg	Glu	Gln	Lys	Ala	Ala	Arg	Arg	Gln	Arg	Glu	Glu
Gln	Gln	Gln	Arg	Gln	Gln	Glu	Gln	Glu	Glu	Arg	Glu	Arg	Glu	Glu
Gln	Arg	Arg	Phe	Ala	Ala	Leu	Ser	Asp	Arg	Glu	Lys	Arg	Ala	Leu
Ala	Ala	Glu	Arg	Arg	Leu	Ala	Ala	Gln	Leu	Gly	Ala	Pro	Thr	Ser
Pro	Ile	Pro	Asp	Ser	Ala	Ile	Val	Asn	Thr	Arg	Arg	Cys	Trp	Ser
Cys	Gly	Ala	Ser	Leu	Gln	Gly	Leu	Thr	Pro	Phe	His	Tyr	Leu	Asp
Phe	Ser	Phe	Cys	Ser	Thr	Arg	Cys	Leu	Gln	Asp	His	Arg	Arg	Gln
Ala	Gly	Arg	Pro	Ser	Ser									

<210> 42

<211> 173

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2013853CD1

<400> 42

Met	Ser	Thr	Met	Gly	Asn	Glu	Ala	Ser	Tyr	Pro	Ala	Glu	Met	Cys
1				5					10					15
Ser	His	Phe	Asp	Asn	Asp	Glu	Ile	Lys	Arg	Leu	Gly	Arg	Arg	Phe
				20					25					30
Lys	Lys	Leu	Asp	Leu	Asp	Lys	Ser	Gly	Ser	Leu	Ser	Val	Glu	Glu
				35					40					45
Phe	Met	Ser	Leu	Pro	Glu	Leu	Arg	His	Asn	Pro	Leu	Val	Arg	Arg
				50					55					60
Val	Ile	Asp	Val	Phe	Asp	Thr	Asp	Gly	Asp	Gly	Glu	Val	Asp	Phe
				65					70					75
Lys	Glu	Phe	Ile	Leu	Gly	Thr	Ser	Gln	Phe	Ser	Val	Lys	Gly	Asp
				80					85					90
Glu	Glu	Gln	Lys	Leu	Arg	Phe	Ala	Phe	Ser	Ile	Tyr	Asp	Met	Asp
				95					100					105
Lys	Asp	Gly	Tyr	Ile	Ser	Asn	Gly	Glu	Leu	Phe	Gln	Val	Leu	Lys
				110					115					120
Met	Met	Val	Gly	Asn	Asn	Leu	Thr	Asp	Trp	Gln	Leu	Gln	Gln	Leu
				125					130					135
Val	Asp	Lys	Thr	Ile	Ile	Ile	Leu	Asp	Lys	Asp	Gly	Asp	Gly	Lys
				140					145					150
Ile	Ser	Phe	Glu	Glu	Phe	Ser	Ala	Val	Val	Arg	Asp	Leu	Glu	Ile
				155					160					165
His	Lys	Lys	Leu	Val	Leu	Ile	Val							

<210> 43

<211> 761

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2284925CD1

<400> 43

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Met Arg Leu Thr Gln Asp Pro Ile Gln Val Leu Leu Ile Phe Ala
 1      5      10
Lys Glu Asp Ser Gln Ser Asp Gly Phe Trp Trp Ala Cys Asp Arg
      20      25      30
Ala Gly Tyr Arg Cys Asn Ile Ala Arg Thr Pro Glu Ser Ala Leu
      35      40      45
Glu Cys Phe Leu Asp Lys His His Glu Ile Ile Val Ile Asp His
      50      55      60
Arg Gln Thr Gln Asn Phe Asp Ala Glu Ala Val Cys Arg Ser Ile
      65      70      75
Arg Ala Thr Asn Pro Ser Glu His Thr Val Ile Leu Ala Val Val
      80      85      90
Ser Arg Val Ser Asp Asp His Glu Glu Ala Ser Val Leu Pro Leu
      95     100     105
Leu His Ala Gly Phe Asn Arg Arg Phe Met Glu Asn Ser Ser Ile
     110     115     120
Ile Ala Cys Tyr Asn Glu Leu Ile Gln Ile Glu His Gly Glu Val
     125     130     135
Arg Ser Gln Phe Lys Leu Arg Ala Cys Asn Ser Val Phe Thr Ala
     140     145     150
Leu Asp His Cys His Glu Ala Ile Glu Ile Thr Ser Asp Asp His
     155     160     165
Val Ile Gln Tyr Val Asn Pro Ala Phe Glu Arg Met Met Gly Tyr
     170     175     180
His Lys Gly Glu Leu Leu Gly Lys Glu Leu Ala Asp Leu Pro Lys
     185     190     195
Ser Asp Lys Asn Arg Ala Asp Leu Leu Asp Thr Ile Asn Thr Cys
     200     205     210
Ile Lys Lys Gly Lys Glu Trp Gln Gly Val Tyr Tyr Ala Arg Arg
     215     220     225
Lys Ser Gly Asp Ser Ile Gln Gln His Val Lys Ile Thr Pro Val
     230     235     240
Ile Gly Gln Gly Gly Lys Ile Arg His Phe Val Ser Leu Lys Lys
     245     250     255
Leu Cys Cys Thr Thr Asp Asn Asn Lys Gln Ile His Lys Ile His
     260     265     270
Arg Asp Ser Gly Asp Asn Ser Gln Thr Glu Pro His Ser Phe Arg
     275     280     285
Tyr Lys Asn Arg Arg Lys Glu Ser Ile Asp Val Lys Ser Ile Ser
     290     295     300
Ser Arg Gly Ser Asp Ala Pro Ser Leu Gln Asn Arg Arg Tyr Pro
     305     310     315
Ser Met Ala Arg Ile His Ser Met Thr Ile Glu Ala Pro Ile Thr
     320     325     330
Lys Val Ile Asn Ile Ile Asn Ala Ala Gln Glu Asn Ser Pro Val
     335     340     345
Thr Val Ala Glu Ala Leu Asp Arg Val Leu Glu Ile Leu Arg Thr
     350     355     360
Thr Glu Leu Tyr Ser Pro Gln Leu Gly Thr Lys Asp Glu Asp Pro
     365     370     375
His Thr Ser Asp Leu Val Gly Gly Leu Met Thr Asp Gly Leu Arg
     380     385     390
Arg Leu Ser Gly Asn Glu Tyr Val Phe Thr Lys Asn Val His Gln
     395     400     405
Ser His Ser His Leu Ala Met Pro Ile Thr Ile Asn Asp Val Pro
     410     415     420
Pro Cys Ile Ser Gln Leu Leu Asp Asn Glu Glu Ser Trp Asp Phe
     425     430     435
Asn Ile Phe Glu Leu Glu Ala Ile Thr His Lys Arg Pro Leu Val

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	440		445		450
Tyr Leu Gly Leu Lys Val Phe Ser Arg		Phe Gly Val Cys Glu Phe			
	455		460		465
Leu Asn Cys Ser Glu Thr Thr Leu Arg		Ala Trp Phe Gln Val Ile			
	470		475		480
Glu Ala Asn Tyr His Ser Ser Asn Ala Tyr		His Asn Ser Thr His			
	485		490		495
Ala Ala Asp Val Leu His Ala Thr Ala Phe		Phe Leu Gly Lys Glu			
	500		505		510
Arg Val Lys Gly Ser Leu Asp Gln Leu Asp		Glu Val Ala Ala Leu			
	515		520		525
Ile Ala Ala Thr Val His Asp Val Asp His		Pro Gly Arg Thr Asn			
	530		535		540
Ser Phe Leu Cys Asn Ala Gly Ser Glu Leu		Ala Val Leu Tyr Asn			
	545		550		555
Asp Thr Ala Val Leu Glu Ser His His Thr		Ala Leu Ala Phe Gln			
	560		565		570
Leu Thr Val Lys Asp Thr Lys Cys Asn Ile		Phe Lys Asn Ile Asp			
	575		580		585
Arg Asn His Tyr Arg Thr Leu Arg Gln Ala		Ile Ile Asp Met Val			
	590		595		600
Leu Ala Thr Glu Met Thr Lys His Phe Glu		His Val Asn Lys Phe			
	605		610		615
Val Asn Ser Ile Asn Lys Pro Met Ala Ala		Glu Ile Glu Gly Ser			
	620		625		630
Asp Cys Glu Cys Asn Pro Ala Gly Lys Asn		Phe Pro Glu Asn Gln			
	635		640		645
Ile Leu Ile Lys Arg Met Met Ile Lys Cys		Ala Asp Val Ala Asn			
	650		655		660
Pro Cys Arg Pro Leu Asp Leu Cys Ile Glu		Trp Ala Gly Arg Ile			
	665		670		675
Ser Glu Glu Tyr Phe Ala Gln Thr Asp Glu		Lys Arg Gln Gly			
	680		685		690
Leu Pro Val Val Met Pro Val Phe Asp Arg		Asn Thr Cys Ser Ile			
	695		700		705
Pro Lys Ser Gln Ile Ser Phe Ile Asp Tyr		Phe Ile Thr Asp Met			
	710		715		720
Phe Asp Ala Trp Asp Ala Phe Ala His Leu		Pro Ala Leu Met Gln			
	725		730		735
His Leu Ala Asp Asn Tyr Lys His Trp Lys		Thr Leu Asp Asp Leu			
	740		745		750
Lys Cys Lys Ser Leu Arg Leu Pro Ser Asp		Ser			
	755		760		

<210> 44

<211> 249

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2376728CD1

<400> 44

Met Val Asp Arg Leu Ala Asn Ser Glu Ala	Asn Thr Arg Arg Ile
1 5	10 15
Ser Ile Val Glu Asn Cys Phe Gly Ala Ala	Gly Gln Pro Leu Thr
20	25 30
Ile Pro Gly Arg Val Leu Ile Gly Glu Gly	Val Leu Thr Lys Leu
35	40 45
Cys Arg Lys Lys Pro Lys Ala Arg Gln Phe	Phe Leu Phe Asn Asp
50	55 60
Ile Leu Val Tyr Gly Asn Ile Val Ile Gln	Lys Lys Lys Tyr Asn
65	70 75
Lys Gln His Ile Ile Pro Leu Glu Asn Val	Thr Ile Asp Ser Ile
80	85 90
Lys Asp Glu Gly Asp Leu Arg Asn Gly Trp	Leu Ile Lys Thr Pro
95	100 105

Thr	Lys	Ser	Phe	Ala	Val	Tyr	Ala	Ala	Thr	Ala	Thr	Glu	Lys	Ser	
				110					115					120	
Glu	Trp	Met	Asn	His	Ile	Asn	Lys	Cys	Val	Thr	Asp	Leu	Leu	Ser	
				125					130					135	
Lys	Ser	Gly	Lys	Thr	Pro	Ser	Asn	Glu	His	Ala	Ala	Val	Trp	Val	
				140					145					150	
Pro	Asp	Ser	Glu	Ala	Thr	Val	Cys	Met	Arg	Cys	Gln	Lys	Ala	Lys	
				155					160					165	
Phe	Thr	Pro	Val	Asn	Arg	Arg	His	His	Cys	Arg	Lys	Cys	Gly	Phe	
				170					175					180	
Val	Val	Cys	Gly	Pro	Cys	Ser	Glu	Lys	Arg	Phe	Leu	Leu	Pro	Ser	
				185					190					195	
Gln	Ser	Ser	Lys	Pro	Val	Arg	Ile	Cys	Asp	Phe	Cys	Tyr	Asp	Leu	
				200					205					210	
Leu	Ser	Ala	Gly	Asp	Met	Ala	Thr	Cys	Gln	Pro	Ala	Arg	Ser	Asp	
				215					220					225	
Ser	Tyr	Ser	Gln	Ser	Leu	Lys	Ser	Pro	Leu	Asn	Asp	Met	Ser	Asp	
				230					235					240	
Asp	Asp	Asp	Asp	Asp	Asp	Ser	Ser	Asp							
				245											

<210> 45

<211> 247

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2790762CD1

<400> 45

Met	Glu	Thr	Asp	Glu	Ser	Pro	Ser	Pro	Leu	Pro	Cys	Gly	Pro	Ala	
1				5					10					15	
Gly	Glu	Ala	Val	Met	Glu	Ser	Arg	Ala	Arg	Pro	Phe	Gln	Ala	Leu	
				20					25					30	
Pro	Arg	Glu	Gln	Ser	Pro	Pro	Pro	Pro	Leu	Gln	Thr	Ser	Ser	Gly	
				35					40					45	
Ala	Glu	Val	Met	Asp	Val	Gly	Ser	Gly	Gly	Asp	Gly	Gln	Ser	Glu	
				50					55					60	
Leu	Pro	Ala	Glu	Asp	Pro	Phe	Asn	Phe	Tyr	Gly	Ala	Ser	Leu	Leu	
				65					70					75	
Ser	Lys	Gly	Ser	Phe	Ser	Lys	Gly	Arg	Leu	Leu	Ile	Asp	Pro	Asn	
				80					85					90	
Cys	Ser	Gly	His	Ser	Pro	Arg	Thr	Ala	Arg	His	Ala	Pro	Ala	Val	
				95					100					105	
Arg	Lys	Phe	Ser	Pro	Asp	Leu	Lys	Leu	Leu	Lys	Asp	Val	Lys	Ile	
				110					115					120	
Ser	Val	Ser	Phe	Thr	Glu	Ser	Cys	Arg	Ser	Lys	Asp	Arg	Lys	Val	
				125					130					135	
Leu	Tyr	Thr	Gly	Ala	Glu	Arg	Asp	Val	Arg	Ala	Glu	Cys	Gly	Leu	
				140					145					150	
Leu	Leu	Ser	Pro	Val	Ser	Gly	Asp	Val	His	Ala	Cys	Pro	Phe	Gly	
				155					160					165	
Gly	Ser	Val	Gly	Asp	Gly	Val	Gly	Ile	Gly	Gly	Glu	Ser	Ala	Asp	
				170					175					180	
Lys	Lys	Asp	Glu	Glu	Asn	Glu	Leu	Asp	Gln	Glu	Lys	Arg	Val	Glu	
				185					190					195	
Tyr	Ala	Val	Leu	Asp	Glu	Leu	Glu	Asp	Phe	Thr	Asp	Asn	Leu	Glu	
				200					205					210	
Leu	Asp	Glu	Glu	Gly	Ala	Gly	Gly	Phe	Thr	Ala	Lys	Ala	Ile	Val	
				215					220					225	
Gln	Arg	Asp	Arg	Val	Asp	Glu	Glu	Ala	Leu	Asn	Phe	Pro	Tyr	Glu	
				230					235					240	
Val	Cys	Trp	Gln	Pro	Leu	Leu									
				245											

<210> 46

<211> 316

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2869164CD1

<400> 46

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Met Ala Glu Ala Ala Leu Glu Ala Val Arg Ser Glu Leu Arg Glu
 1          5          10          15
Phe Pro Ala Ala Ala Arg Glu Leu Cys Val Pro Leu Ala Val Pro
          20          25          30
Tyr Leu Asp Lys Pro Pro Thr Pro Leu His Phe Tyr Arg Asp Trp
          35          40          45
Val Cys Pro Asn Arg Pro Cys Ile Ile Arg Asn Ala Leu Gln His
          50          55          60
Trp Pro Ala Leu Gln Lys Trp Ser Leu Pro Tyr Phe Arg Ala Thr
          65          70          75
Val Gly Ser Thr Glu Val Ser Val Ala Val Thr Pro Asp Gly Tyr
          80          85          90
Ala Asp Ala Val Arg Gly Asp Arg Phe Met Met Pro Ala Glu Arg
          95          100          105
Arg Leu Pro Leu Ser Phe Val Leu Asp Val Leu Glu Gly Arg Ala
          110          115          120
Gln His Pro Gly Val Leu Tyr Val Gln Lys Gln Cys Ser Asn Leu
          125          130          135
Pro Ser Glu Leu Pro Gln Leu Leu Pro Asp Leu Glu Ser His Val
          140          145          150
Pro Trp Ala Ser Glu Ala Leu Gly Lys Met Pro Asp Ala Val Asn
          155          160          165
Phe Trp Leu Gly Glu Ala Ala Ala Val Thr Ser Leu His Lys Asp
          170          175          180
His Tyr Glu Asn Leu Tyr Cys Val Val Ser Gly Glu Lys His Phe
          185          190          195
Leu Phe His Pro Pro Ser Asp Arg Pro Phe Ile Pro Tyr Glu Leu
          200          205          210
Tyr Thr Pro Ala Thr Tyr Gln Leu Thr Glu Glu Gly Thr Phe Lys
          215          220          225
Val Val Asp Glu Glu Ala Met Glu Lys Val Pro Trp Ile Pro Leu
          230          235          240
Asp Pro Leu Ala Pro Asp Leu Ala Arg Tyr Pro Ser Tyr Ser Gln
          245          250          255
Ala Gln Ala Leu Arg Cys Thr Val Arg Ala Gly Glu Met Leu Tyr
          260          265          270
Leu Pro Ala Leu Trp Phe His His Val Gln Ser Gln Gly Cys
          275          280          285
Ile Ala Val Asn Phe Trp Tyr Asp Met Glu Tyr Asp Leu Lys Tyr
          290          295          300
Ser Tyr Phe Gln Leu Leu Asp Ser Leu Thr Lys Ala Ser Gly Leu
          305          310          315

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Asp

<210> 47

<211> 334

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3317629CD1

<400> 47

```

Met Thr Arg Ser Leu Phe Lys Gly Asn Phe Trp Ser Ala Asp Ile
 1          5          10          15
Leu Ser Thr Ile Gly Tyr Asp Asn Ile Ile Gln His Leu Asn Asn
          20          25          30
Gly Arg Lys Asn Cys Lys Glu Phe Glu Asp Phe Leu Lys Glu Arg
          35          40          45

```

```

Ala Ala Ile Glu Glu Arg Tyr Gly Lys Asp Leu Leu Asn Leu Ser
      50      55      60
Arg Lys Lys Pro Cys Gly Gln Ser Glu Ile Asn Thr Leu Lys Arg
      65      70      75
Ala Leu Glu Val Phe Lys Gln Gln Val Asp Asn Val Ala Gln Cys
      80      85      90
His Ile Gln Leu Ala Gln Ser Leu Arg Glu Glu Ala Arg Lys Met
      95     100     105
Glu Glu Phe Arg Glu Lys Gln Lys Leu Gln Arg Lys Lys Thr Glu
     110     115     120
Leu Ile Met Asp Ala Ile His Lys Gln Lys Ser Leu Gln Phe Lys
     125     130     135
Lys Thr Met Asp Ala Lys Lys Asn Tyr Glu Gln Lys Cys Arg Asp
     140     145     150
Lys Asp Glu Ala Glu Gln Ala Val Ser Arg Ser Ala Asn Leu Val
     155     160     165
Asn Pro Lys Gln Gln Glu Lys Leu Phe Val Lys Leu Ala Thr Ser
     170     175     180
Lys Thr Ala Val Glu Asp Ser Asp Lys Ala Tyr Met Leu His Ile
     185     190     195
Gly Thr Leu Asp Lys Val Arg Glu Glu Trp Gln Ser Glu His Ile
     200     205     210
Lys Ala Cys Glu Ala Phe Glu Ala Gln Glu Cys Glu Arg Ile Asn
     215     220     225
Phe Phe Arg Asn Ala Leu Trp Leu His Val Asn Gln Leu Ser Gln
     230     235     240
Gln Cys Val Thr Ser Asp Glu Met Tyr Glu Gln Val Arg Lys Ser
     245     250     255
Leu Glu Met Cys Ser Ile Gln Arg Asp Ile Glu Tyr Phe Val Asn
     260     265     270
Gln Arg Lys Thr Gly Gln Ile Pro Pro Ala Pro Ile Met Tyr Glu
     275     280     285
Asn Phe Tyr Ser Ser Gln Lys Asn Ala Val Pro Ala Gly Lys Ala
     290     295     300
Thr Gly Pro Asn Leu Ala Arg Arg Gly Pro Leu Pro Ile Pro Lys
     305     310     315
Ser Ser Pro Asp Asp Pro Asn Tyr Ser Leu Val Asp Asp Tyr Ser
     320     325     330
Leu Leu Tyr Gln

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<210> 48

<211> 113

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3870488CD1

<400> 48

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Met Asp Pro Lys Leu Leu Lys Gln Leu Arg Lys Ala Glu Lys Ala
  1      5      10
Glu Arg Glu Phe Arg Lys Lys Phe Lys Phe Glu Gly Glu Ile Val
     20     25     30
Val His Thr Lys Met Met Ile Asp Pro Asn Ala Lys Thr Arg Arg
     35     40     45
Gly Gly Gly Lys His Leu Gly Ile Arg Arg Gly Glu Ile Leu Glu
     50     55     60
Val Ile Glu Phe Thr Ser Asn Glu Glu Met Leu Cys Arg Asp Pro
     65     70     75
Lys Gly Lys Tyr Gly Tyr Val Pro Arg Thr Ala Leu Leu Pro Leu
     80     85     90
Glu Thr Glu Val Tyr Asp Asp Val Asp Phe Cys Asp Pro Leu Glu
     95    100    105
Asn Gln Pro Leu Pro Leu Gly Arg
     110

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<210> 49

<211> 264
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 3886318CD1

<400> 49
 Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu
 1 5 10 15
 Ser Ile Ser Lys Arg Glu Gln Leu Glu Gln Gln Val Pro Glu Asn
 20 25 30
 Tyr Phe Tyr Val Pro Asp Leu Gly Gln Val Pro Glu Ile Asp Val
 35 40 45
 Pro Ser Tyr Leu Pro Asp Leu Pro Gly Ile Ala Asn Asp Leu Met
 50 55 60
 Tyr Ile Ala Asp Leu Gly Pro Gly Ile Ala Pro Ser Ala Pro Gly
 65 70 75
 Thr Ile Pro Glu Leu Pro Thr Phe His Thr Glu Val Ala Glu Pro
 80 85 90
 Leu Lys Ala Asp Leu Gln Asp Gly Val Leu Thr Pro Pro Pro Pro
 95 100 105
 Pro Pro Pro Pro Pro Pro Ala Pro Glu Val Leu Ala Ser Ala Pro
 110 115 120
 Pro Leu Pro Pro Ser Thr Ala Ala Pro Val Gly Gln Gly Ala Arg
 125 130 135
 Gln Asp Asp Ser Ser Ser Ser Ala Ser Pro Ser Val Gln Gly Ala
 140 145 150
 Pro Arg Glu Val Val Asp Pro Ser Gly Gly Arg Ala Thr Leu Leu
 155 160 165
 Glu Ser Ile Arg Gln Ala Gly Gly Ile Gly Lys Ala Lys Leu Arg
 170 175 180
 Ser Met Lys Glu Arg Lys Leu Glu Lys Lys Gln Gln Lys Glu Gln
 185 190 195
 Glu Gln Val Arg Ala Thr Ser Gln Gly Gly His Leu Met Ser Asp
 200 205 210
 Leu Phe Asn Lys Leu Val Met Arg Arg Lys Gly Ile Ser Gly Lys
 215 220 225
 Gly Pro Gly Ala Gly Glu Gly Pro Gly Gly Ala Phe Ala Arg Val
 230 235 240
 Ser Asp Ser Ile Pro Pro Leu Pro Pro Pro Gln Gln Pro Gln Ala
 245 250 255
 Glu Glu Asp Glu Asp Asp Trp Glu Ser
 260

<210> 50
 <211> 185
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4043934CD1

<400> 50
 Met Gly Gln Cys Leu Arg Tyr Gln Met His Trp Glu Asp Leu Glu
 1 5 10 15
 Glu Tyr Gln Ala Leu Thr Phe Leu Thr Arg Asn Glu Ile Leu Cys
 20 25 30
 Ile His Asp Thr Phe Leu Lys Leu Cys Pro Pro Gly Lys Tyr Tyr
 35 40 45
 Lys Glu Ala Thr Leu Thr Met Asp Gln Val Ser Ser Leu Pro Ala
 50 55 60
 Leu Arg Val Asn Pro Phe Arg Asp Arg Ile Cys Arg Val Phe Ser
 65 70 75
 His Lys Gly Met Phe Ser Phe Glu Asp Val Leu Gly Met Ala Ser
 80 85 90

```

Val Phe Ser Glu Gln Ala Cys Pro Ser Leu Lys Ile Glu Tyr Ala
      95      100      105
Phe Arg Ile Tyr Asp Phe Asn Glu Asn Gly Phe Ile Asp Glu Glu
      110      115      120
Asp Leu Gln Arg Ile Ile Leu Arg Leu Leu Asn Ser Asp Asp Met
      125      130      135
Ser Glu Asp Leu Leu Met Asp Leu Thr Asn His Val Leu Ser Glu
      140      145      150
Ser Asp Leu Asp Asn Asp Asn Met Leu Ser Phe Ser Glu Phe Glu
      155      160      165
His Ala Met Ala Lys Ser Pro Asp Phe Met Tyr Ser Phe Arg Ile
      170      175      180
Arg Phe Trp Gly Cys
      185

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<210> 51
 <211> 72
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4371445CD1

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<400> 51
Met Phe Thr Ile Ile Phe Pro Val Cys Lys Asn Ser Met Pro Val
      1      5      10      15
Lys Lys Thr Asp Thr Asp Arg Ala Leu Ser Leu Leu Glu Glu Tyr
      20      25      30
Cys Lys Lys Leu Arg Lys Pro Glu Glu Gln Leu Leu Lys Asn Ala
      35      40      45
Val Lys Lys Val Met Gly Ile Phe Lys Ser Ser Leu Phe Gln Ala
      50      55      60
Leu Leu Gly Met Tyr Tyr Glu Ser Tyr Ser Ser Phe
      65      70

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<210> 52
 <211> 434
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 5527925CD1

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<400> 52
Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly
      1      5      10      15
Gly Lys Leu Arg Arg Gly Leu Ala Val Ser Arg Gln Ala Val Arg
      20      25      30
Ser Pro Gly Pro Leu Ala Ala Ala Val Ala Gly Ala Ala Leu Ala
      35      40      45
Gly Ala Gly Ala Ala Trp His His Ser Arg Val Ser Val Ala Ala
      50      55      60
Arg Asp Gly Ser Phe Thr Val Ser Ala Gln Lys Asn Val Glu His
      65      70      75
Gly Ile Ile Tyr Ile Gly Lys Pro Ser Leu Arg Lys Gln Arg Phe
      80      85      90
Met Gln Phe Ser Ser Leu Glu His Glu Gly Glu Tyr Tyr Met Thr
      95      100      105
Pro Arg Asp Phe Leu Phe Ser Val Met Phe Glu Gln Met Glu Arg
      110      115      120
Lys Thr Ser Val Lys Lys Leu Thr Lys Lys Asp Ile Glu Asp Thr
      125      130      135
Leu Ser Gly Ile Gln Thr Ala Gly Cys Gly Ser Thr Phe Phe Arg
      140      145      150
Asp Leu Gly Asp Lys Gly Leu Ile Ser Tyr Thr Glu Tyr Leu Phe
      155      160      165
Leu Leu Thr Ile Leu Thr Lys Pro His Ser Gly Phe His Val Ala

```

	170		175		180
Phe Lys Met Leu	Asp Thr Asp Gly Asn	Glu Met Ile Glu Lys	Arg		
	185		190		195
Glu Phe Phe Lys	Leu Gln Lys Ile Ile	Ser Lys Gln Asp Asp	Leu		
	200		205		210
Met Thr Val Lys	Thr Asn Glu Thr Gly	Tyr Gln Glu Ala Ile	Val		
	215		220		225
Lys Glu Pro Glu	Ile Asn Thr Thr Leu	Gln Met Arg Phe Phe	Gly		
	230		235		240
Lys Arg Gly Gln	Arg Lys Leu His Tyr	Lys Glu Phe Arg Arg	Phe		
	245		250		255
Met Glu Asn Leu	Gln Thr Glu Ile Gln	Glu Met Glu Phe Leu	Gln		
	260		265		270
Phe Ser Lys Gly	Leu Ser Phe Met Arg	Lys Glu Asp Phe Ala	Glu		
	275		280		285
Trp Leu Leu Phe	Phe Thr Asn Thr Glu	Asn Lys Asp Ile Tyr	Trp		
	290		295		300
Lys Asn Val Arg	Glu Lys Leu Ser Ala	Gly Glu Ser Ile Ser	Leu		
	305		310		315
Asp Glu Phe Lys	Ser Phe Cys His Phe	Thr Thr His Leu Glu	Asp		
	320		325		330
Phe Ala Ile Ala	Met Gln Met Phe Ser	Leu Ala His Arg Pro	Val		
	335		340		345
Arg Leu Ala Glu	Phe Lys Arg Ala Val	Lys Val Ala Thr Gly	Gln		
	350		355		360
Glu Leu Ser Asn	Asn Ile Leu Asp Thr	Val Phe Lys Ile Phe	Asp		
	365		370		375
Leu Asp Gly Asp	Glu Cys Leu Ser His	Glu Glu Phe Leu Gly	Val		
	380		385		390
Leu Lys Asn Arg	Met His Arg Gly Leu	Trp Val Pro Gln His	Gln		
	395		400		405
Ser Ile Gln Glu	Tyr Trp Lys Cys Val	Lys Lys Glu Ser Ile	Lys		
	410		415		420
Gly Val Lys Glu	Val Trp Lys Gln Ala	Gly Lys Gly Leu Phe			
	425		430		

<210> 53

<211> 1629

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 129042CB1

<400> 53

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gcgacctgta tgaggaggag gaggaggagg atgtgaagat ggccggacgtg cagatgctgc 60
tggaagagga aatccccggg ggccgccggg ccctcttcga cagctacaca aatctggaac 120
gggtggccga ttactgcgag aacaactaca tacagtcagc agataagcag agagccctag 180
aagaaaccaa agcctacacc acccaatcct tagcaagtgt tgcctatctg ataaacacct 240
tgGCCaACAA tGtCctGcag atGctGgata tccaggcatc ccagctacga aggatggaat 300
cttcaatcaa tcatatttca caaacagttg atattcataa agagaaagtt gcaagaagag 360
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<212> DNA

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<223> Incyte ID No: 2658329CB1

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<213> Homo sapiens

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 <213> Homo sapiens

<220>
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 <223> Incyte ID No: 3315012CB1

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<211> 1156

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 4155412CB1

<400> 68

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<211> 1981

<212> DNA

<213> Homo sapiens

<220>

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<223> Incyte ID No: 4831840CB1

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<210> 70

<211> 1832

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5676581CB1

<400> 70

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<210> 71

<211> 1772
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 034159CB1

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<210> 72
 <211> 1488
 <212> DNA
 <213> Homo sapiens

<220>
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<210> 73
 <211> 2430
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1358940CB1

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<210> 74
 <211> 1411
 <212> DNA
 <213> Homo sapiens

<220>

<221> misc_feature
 <223> Incyte ID No: 1682320CB1

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 ttattttgtct cccaacccca gagcttcact tgctccttca cttcccagtt ccgcaagaac 420
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 gggcgctcta gctcatgctt gtaatccca c 1411

<210> 75
 <211> 653
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1728263CB1

<400> 75
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 aagtatttaa agcatgtgat gaagatcaca aaggatatct cagcagagag gactttaaaa 180
 ctgctgttgt aatgctgttt gggatcaagc cctccaagat agaagtggat tctgtgatgt 240
 cttcaataaa tccaaatact tctgggtatat tactcgaggg gtttttaaat attgtcagga 300
 aaaagaagga agctcaacga tatcggaacg aagtaagaca catcttcaca gcctttgaca 360
 cctactatcg tggattttta acttttgaag atttcaaaaa agcatttagg caggtggctc 420
 ccaaattacc ggaaaggact gttcttgagg tattcaggga agtagatcga gattcagatg 480
 gtcacgtcag ctttagagac ttggaatatg ccctgaacta tggacagaag gaagcctaac 540
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<210> 76
 <211> 1448
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1867626CB1

<400> 76
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 tggattttac aagagagaaa tcattttacc taagagaact aattgaattg gcagcatcct 180
 tgaaatacct ccggacaagg atctgggggt ggggggtggaa aagcaactgc gaaatagcag 240
 acggagaaat tcctttggaa gttattccgt agcataagag ctgaaacttc agagcaagtt 300
 ttcattggggc aaaatggggg aacaacctat cttcagcact cgagctcatg tcttccaaat 360

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gatatttgaa	ctaacagaat	tacgagataa	cttggccaag	ctactagaat	gcagctaagg	1380
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tagctctg						1448

<210> 77

<211> 1538

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1990126CB1

<400> 77

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gcaccttcct	cagtcgcgcc	gtgcagttca	cagaagaaaa	gcttggccag	gctgagaaga	180
cagaatttga	tgctcactta	gagaacctcc	ttagcaaaagc	tgaatgtacc	aaaatatgga	240
cagaaaaaat	aatgaaacaa	actgaagtgt	tattgcagcc	aaatccaaat	gccaggatag	300
aagaatttgt	ttatgagaaa	ctggatagaa	aagctccaag	tcgtataaac	aaccagaac	360
ttttgggaca	atatatgatt	gatgcaggga	ctgagtttgg	cccaggaaca	gcttatggta	420
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<210> 78

<211> 998

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2104180CB1

<400> 78

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<210> 79

<211> 1086

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2122241CB1

<400> 79

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ccatttggga ttgccgcca ctgacaactt agtagggctt tcattataag caggcttgag 180
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cacctgacag aagggaactat tcctagttaa tgaggtggtt aaggatatcg gtggggtggg 420
ctggagcggg gtcgggttag gtctgagaga aggcctcgca caaaacactg taaaaacccg 480
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tttctcaaat atacctactg gattaattta tggcaataaa attttttttt gtctttttaa 1080
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<210> 80

<211> 2323

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2580428CB1

<400> 80

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ccctgctgtc agtgcgcttg cgcgcgggtc cggcgccgag gttcttgact gctgtgccgg 180
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ctggaactcc atcccacta caagacatgg ggtccggagc aggtgtgctc cttcctcagg 360
cgcggtggct ttgaagagcc ggtgctgctg aagaacatcc gagaaaatga aatcacaggc 420
gcattactgc cttgtcttga tgagtctcgt tttgaaaatc ttggagtaag ttccctgggg 480
gagaggaaga agctgcttag ttatatccag cgattggttc aaatccacgt tgatacaatg 540

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aaggtaatta atgatcctat ccatggccac attgagctcc accctctcct cgtccgaatc 600
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gtttttccag gagcttcaca caatcgattt gagcatagtc taggggtggg gtatctagca 720
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<210> 81
 <211> 669
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 3397189CB1

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gagaccattc ccaaattgga ggtcatcatt catttaccaa gtgtttcctt catgccagc 600
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669

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<210> 82
 <211> 1606
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4881249CB1

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<400> 82
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gaggtgcagg ggaagtacgt gaagaaggag acgtgcctc tgcttcggaa tcttatgcct 180

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<211> 1079

<212> DNA

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<212> DNA
<213> Homo sapiens

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<220>
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<212> DNA
<213> Homo sapiens

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<220>
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